TOXICOLOGICAL PROFILE FOR ALPHA-, BETA-, GAMMA-, and DELTA-HEXACHLOROCYCLOHEXANE

Prepared by:

Research Triangle Institute
Under Contract No. 205-93-0606

Prepared for:

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

July 1999

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UPDATE STATEMENT

A Toxicological Profile for hexachlorocyclohexane was released in May 1997. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Jeffrey P. Koplan, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure*, by *type of health effect* (death, systemic, immunologic, reproductive), and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

> ***NOTE:*** Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 2.6 Children's Susceptibility
Section 5.6 Exposures of Children

Other Sections of Interest:

Section 2.7 Biomarkers of Exposure and Effect
Section 2.10 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-888-42-ATSDR or 404-639-6357 ***Fax:*** 404-639-6359
E-mail: ***atsdric@cdc.gov*** ***Internet:*** ***http://www.atsdr.cdc.gov***

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity;* and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact:* NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. *Contact:* NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

*The National Institute of Environmental Health Sciences (*NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: ***aoec@dgs.dgsys.com*** • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-228-6850 • FAX: 847-228-1856.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying endpoints.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for hexachlorocyclohexane. The panel consisted of the following members:

1. Dr. Carson Conaway, Research Scientist, American Health Foundation, Valhalla, New York

2. Dr. Arthur Gregory, Private Consultant, Luray, Virginia

3. Dr. Donald Morgan, Private Consultant, Cedar Rapids, Iowa

4. James E. Klaunig, Ph.D., Professor and Director of Toxicology, Department of Pharmacology and Toxicology, Indiana University College of Medicine

5. Christine Ecles, Ph.D., Associate Professor, University of Maryland, School of Pharmacy, Baltimore, Maryland

These experts collectively have knowledge of hexachlorocyclohexane's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about hexachlorocyclohexane and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Hexachlorocyclohexane has been found in at least 144 of the 1,467 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which hexachlorocyclohexane is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact.

If you are exposed to hexachlorocyclohexane, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS HEXACHLOROCYCLOHEXANE?

Hexachlorocyclohexane (HCH), also known as benzene hexachloride (BHC), is a synthetic chemical that exists in eight chemical forms called isomers. The different isomers are named according to the position of the hydrogen atoms in the structure of the chemical. One of these forms, gamma-HCH (or γ-HCH, commonly called lindane), is produced and used as an insecticide on fruit, vegetables, and forest crops. It is also used in the United States and in many other countries as a topical treatment for head and body lice and scabies, a contagious skin

disease caused by mites. It is a white solid whose vapor may evaporate into the air. The vapor is colorless and has a slight musty odor when it is present at 12 or more parts HCH per million parts air (ppm). γ-HCH has not been produced in the United States since 1976. However, imported γ-HCH is available in the United States for insecticide use as a dust, powder, liquid, or concentrate. It is also available as a lotion, cream, or shampoo to control scabies and head lice.

Technical-grade HCH, a mixture of several chemical forms of HCH, was also once used as an insecticide in the United States and typically contained about 10–15% γ-HCH as well as the alpha (α), beta (β), delta (δ), and epsilon (ε) forms of HCH. Virtually all of the insecticidal properties reside in the gamma isomer. Technical-grade HCH has not been produced in the United States since 1983. In addition, isomers of HCH other than γ-HCH may not be made or used commercially in the United States.

The scope of this profile includes information on technical-grade HCH, as well as the alpha (α), beta (β), gamma (γ), and delta (δ) isomers. Available information on the epsilon (ε) isomer is limited and is not included in this profile. Chapter 3 contains more information on the chemical and physical properties of HCH.

1.2 WHAT HAPPENS TO HEXACHLOROCYCLOHEXANE WHEN IT ENTERS THE ENVIRONMENT?

Although technical-grade HCH is no longer used as an insecticide in the United States, α-, β-, γ-, and δ-HCH have been found in the soil and surface water at hazardous waste sites. In air, the different forms of HCH can be present as a vapor or attached to small particles such as soil and dust; the particles may be removed from the air by rain. γ-HCH can remain in the air for as long as 17 weeks depending on moisture in the air and temperature. In soil, sediments, and water, it is broken down to less toxic substances by algae, fungi, and bacteria. In general, HCH isomers are broken down quickly in water; in natural water samples, γ-HCH does not remain for much longer than 30 days. γ-HCH is not generally found in drinking water. The length of time that HCH isomers remain in soil is not known. Chapter 5 contains more information about the presence of HCH in the environment.

1.3 HOW MIGHT I BE EXPOSED TO HEXACHLOROCYCLOHEXANE?

Humans can be exposed to α-, β-, γ-, and δ-HCH in workplace air; in the air surrounding factories where HCH is used; or by eating plants, meat, milk, or water that contain forms of HCH. According to the National Occupational Exposure Survey from 1981–1983, about 15,000 workers were exposed to HCH (NOES 1983). At spill and dump sites, HCH isomers can enter the air from contaminated soil and from plants grown in contaminated soil. They can also be washed from the soil and plants into surface water. Typically, people are not exposed to the α, β, and δ forms of HCH separately, but to γ-HCH only or to technical-grade HCH, which contains a mixture of the isomers. People are exposed to γ-HCH when it is applied to the skin as a lotion or shampoo to control lice and scabies. The most severe exposures to lindane have occurred in workers who make lindane or in other workplaces such as fertilizer manufacturing sites.

For more information on exposure to HCH, refer to Chapter 5.

1.4 HOW CAN HEXACHLOROCYCLOHEXANE ENTER AND LEAVE MY BODY?

γ-HCH and the other isomers of HCH can enter your body when you eat food or drink water contaminated with HCH. Inhaling air contaminated with γ-HCH or other isomers of HCH can also lead to entry of these chemicals into the lungs. γ-HCH can be absorbed through the skin when it is used as a lotion to control scabies or body lice. In general, HCH isomers and the products formed from them in the body can be temporarily stored in body fat. Among the HCH isomers, β-HCH leaves the body the most slowly. α-HCH, δ-HCH, and γ-HCH, and the products formed from them in the body, are more rapidly excreted in the urine; small amounts leave in the feces and expired air. HCH breaks down in the body to many other substances; these include various chlorophenols, some of which have toxic properties. Chapter 2 gives more information on how HCH enters and leaves the body.

1.5 HOW CAN HEXACHLOROCYCLOHEXANE AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

In humans, the effects of breathing toxic amounts of γ-HCH and/or α-, β-, and δ-HCH can result in blood disorders, dizziness, headaches, and possible changes in the levels of sex hormones in the blood. These effects have occurred in workers exposed to HCH vapors during pesticide manufacturing. People who have swallowed large amounts have had seizures; some have died. A few people, who have used very large amounts of γ-HCH or used it frequently on their skin, have developed blood disorders or seizures. However, no cause-and-effect relationship between exposure to γ-HCH and blood disorders in humans has been established. Animals that have been fed γ- and α-HCH have had convulsions, and animals fed β-HCH have become comatose. All isomers can produce liver and kidney effects. Reduced ability to fight infection was reported in animals fed γ-HCH, and injury to the ovaries and testes was reported in animals given γ-HCH or β-HCH. HCH isomers are changed by the body into other chemical products, some of which may be responsible for the harmful effects. Long-term oral administration of α-HCH, β-HCH, γ-HCH, or technical-grade HCH to laboratory rodents has been reported to result in liver cancer. The Department of Health and Human Services (DHHS) has determined that HCH may reasonably be anticipated to cause cancer in humans. Chapter 2 gives more information about the health effects of HCH isomers.

1.6 HOW CAN HEXACHLOROCYCLOHEXANE AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans.

The most likely source of exposure for children is from the use of shampoos and lotions containing HCH for the treatment of lice. HCH has also been found as a residue in food products; β-HCH isomer accumulates in animal tissue. In the body, α-, δ-, and γ-HCH are rapidly broken down and excreted. Although HCH is a restricted use pesticide in the U.S., children could be exposed from eating foods grown in areas where HCH is still used or misused as a pesticide. HCH has also been detected in breast milk and this is a possible exposure pathway for infants and children.

Limited information is available on the specific health effects resulting from HCH exposure in children. Health effects observed in adults should also be of potential concern in children. Children can experience convulsions from exposure to γ-HCH. Accidentally eating enough γ-HCH can kill a child. It is not known for sure whether children are more susceptible than adults to health effects from exposure γ-HCH. However, a study performed on rabbits showed that young animals had higher death rates and greater sensitivity than adults when γ-HCH was applied to skin.

We do not know whether HCH causes birth defects in humans. Technical grade and γ-HCH do not cause significant birth defects in animals. Animals fed γ-HCH during pregnancy had an increased number of fetuses with extra ribs, a normal variation. HCH has been shown to cross the placenta in pregnant women. HCH is likely to be stored in fat. It has been measured in skin lipids and breast milk. In studies on rats, HCH has been shown to pass from the mother to newborns in the dam's milk and causes neurological and hormonal effects. The male offspring of female rats that had been fed HCH during lactation demonstrated a 50% reduction in testosterone levels and reduced testicular weight in adolescence and adulthood.

More information on how HCH can affect the health of children can be found in Sections 2.6 and 5.6.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO HEXACHLOROCYCLOHEXANE?

If your doctor finds that you have been exposed to significant amounts of hexachlorocyclo-hexane, ask if children may also be exposed. When necessary your doctor may need to ask your state department of public health to investigate.

There are two primary pathways through which families can be exposed to HCH. γ-HCH, also known as lindane is used in shampoos and lotions for the treatment of lice. It is normally safe if used as directed, but is often misused. If you use shampoos or lotions containing γ-HCH, follow the directions carefully. Products containing γ-HCH (lindane) should never be used on infants. Shampoos or lotions that contain lindane should be stored out of the reach of young children to prevent accidental poisonings. You may expose your child to lindane if you use lindane to treat lice on your child's head. There are alternatives that do not involve the use of lindane.

γ-HCH is a restricted use pesticide. Its allowed use around the home is limited to structural treatments, animal shampoos, and animal flea dusts. Your children may be exposed to HCH if an unqualified person applies pesticides containing it around your home. In some cases, the improper use of pesticides banned for use in homes has turned homes into hazardous waste sites. Make sure that any person you hire is licensed and certified to apply pesticides. Your state licenses each person who is qualified to apply pesticides according to EPA standards and further certifies each person who is qualified to apply "restricted use" pesticides. Ask to see the license and certification. Also ask for the brand name of the pesticide, a Material Safety Data Sheet (MSDS), the name of the product's active ingredients, and the EPA registration number. This information can be important if you or your family react to the product.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO HEXACHLOROCYCLOHEXANE?

HCH isomers can be measured in the blood, urine, and semen of exposed persons. Samples of these fluids can be collected in a doctor's office and sent to a laboratory that has the special equipment needed to measure the levels of HCH. Although the amount of HCH isomers in blood, urine, or semen can be measured, it is usually not possible to determine the environmental levels to which the person was exposed or to predict the health effects that are likely to occur from specific concentrations. The products of HCH that are formed in the body and then found in the urine have also been measured to find out whether a person was exposed to HCH. However, this method cannot yet be used to determine exposure to HCH alone because other environmental chemicals produce the same end products. Chapter 6 contains more information on ways to measure HCH in human blood and tissues.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals, then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for HCH include the following:

γ-HCH is categorized by EPA as a restricted use pesticide. It can only be used by certified applicators. EPA has also recommended guidelines on how much HCH can be present in drinking water for specific periods of time without producing health effects. EPA advises that children should not have more than 1.2 milligrams per liter of water (mg/L) in 10 days or more than 0.033 mg/L per day for long-term (7 years) exposure. For long-term exposure in adults, EPA recommends that there should not be more than 0.12 mg/L in drinking water. The EPA has classified α-HCH and technical-grade HCH as probable human carcinogens. β-HCH has been classified as a possible human carcinogen, while δ-HCH has been designated as not classifiable for human cancer. IARC has classified HCH as a possible human carcinogen. EPA has classified HCH as a hazardous waste that must meet certain disposal requirements.

OSHA regulates levels of γ-HCH in the workplace. The maximum allowable amount in workroom air during an 8-hour workday in a 40-hour workweek is 0.5 mg per cubic meter of air.

Chapter 7 contains more information about regulations and guidelines concerning HCH.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: 1-800-447-1544
Fax: (404) 639-6359

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 487-4650

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of hexachlorocyclohexane (HCH). It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure—inhalation, oral, and dermal; and then by health effect—death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods—acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in

determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of hexachlorocyclohexane are indicated in Tables 2-1 and 2-2 and Figures 2-1 and 2-2.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for hexachlorocyclohexane. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

HCH exists as several isomers. The four major isomers discussed in this profile are alpha-HCH (α-HCH), beta-HCH (β-HCH), gamma-HCH (γ-HCH), and delta-HCH (δ-HCH). γ-HCH is also commonly known as lindane. Technical-grade HCH consists of at least 5 isomers (approximately 60–70% α-HCH, 5–12% β-HCH, 10–15% γ-HCH, 6–10% δ-HCH, and 3–4% ε-HCH). The toxicity of the isomers varies. With respect to acute exposure, γ-HCH is the most toxic, followed by α-, δ-, and β-HCH. With chronic exposure, however, β-HCH is the most toxic followed by α-, γ-, and δ-HCH. With chronic exposures, the increased toxicity of β-HCH is probably due to its longer biological half-life in the body and its accumulation in the body over time.

2.2.1 Inhalation Exposure

Studies examining the inhalation toxicity of HCH in humans are limited. Most of the available information is from case reports of acute poisoning in the home following the use of γ-HCH vaporizers, whereby γ-HCH pellets are vaporized by electrical warming of a ceramic jacket, and from studies of workers engaged in the manufacture and formulation of pesticides and fertilizers. Limitations inherent in these reports or studies include unquantified exposure concentrations and concomitant exposure to HCH mixtures, pyrolysis products from vaporizers, and other pesticides and chemicals. Studies that provide levels of significant exposure for inhalation exposure to γ-HCH are shown in Table 2-1 and Figure 2-1.

2.2.1.1 Death

γ-HCH was once used in vaporizers, resulting in human exposure to unspecified levels via inhalation and dermal routes. Occasional deaths associated with the use of this product for several months or years have been
reported, but in no case is it clear that γ-HCH was responsible for the deaths (Loge 1965). No human deaths from inhalation exposure to other isomers have been reported.

An acute study with rats exposed to nose-only inhalation of lindane aerosol for 4 hours, followed by a 22-day observation period, estimated the acute LC_{50} to be 1,560 mg/m^3 (Ullmann 1986b). Rats inhaling up to 603 mg/m^3 lindane aerosol for 4 hours in whole-body exposure chambers exhibited no mortality throughout the 14-day observation period (Oldiges et al. 1980). However, the particle sizes produced in aerosol studies are variable, and there is a potential for dermal and oral exposures since the animals could lick their fur.

TABLE 2-1. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Inhalation

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference
ACUTE EXPOSURE							
Death							
1	Rat (Wistar)	4 hr				1560 (LC_{50})	Ullmann 1986b
2	Mouse (CD-1)	1 wk 5 d/wk 6 hr/d				10 (16% mortality)	Klonne and Kintigh 1988
Systemic							
3	Rat (Wistar)	4 hr	Resp	603			Oldiges et al. 1980
			Hepatic	603			
			Renal	603			
Neurological							
4	Rat (Wistar)	4 hr			101 (sedation)	642 (restlessness, excitation, ataxia)	Ullmann 1986b
INTERMEDIATE EXPOSURE							
Death							
5	Mouse (CD-1)	14 wk 5 d/wk 6 hr/d				1.0 (2% mortality)	Klonne and Kintigh 1988

Figure 2-1. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Inhalation (cont.)

Intermediate (15-364 days)

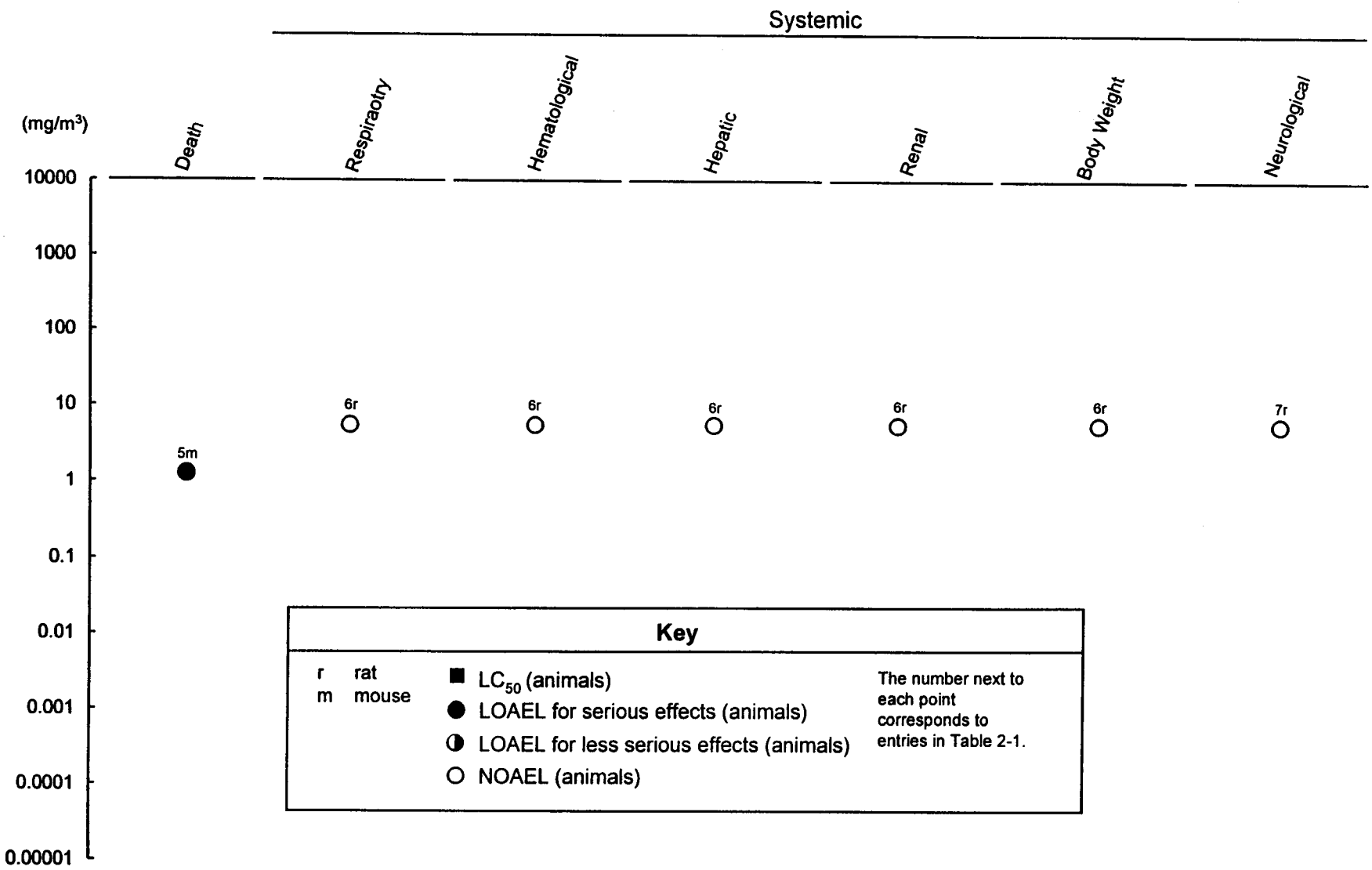


TABLE 2-1. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference
					Less serious (mg/m3)	Serious (mg/m3)	
Systemic							
6	Rat (Wistar)	90 d 6 hr/d	Resp	5			Oldiges et al. 1983
			Hemato	5			
			Hepatic	5			
			Renal	5			
			Bd Wt	5			
Neurological							
7	Mouse (CD-1)	14 wk 5 d/wk 6 hr/d		5			Klonne and Kintigh 1988

[a]The number corresponds to entries in Figure 2-1.

Bd Wt = body weight; d = day(s); Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s).

Figure 2-1. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Inhalation

Acute (≤14 days)

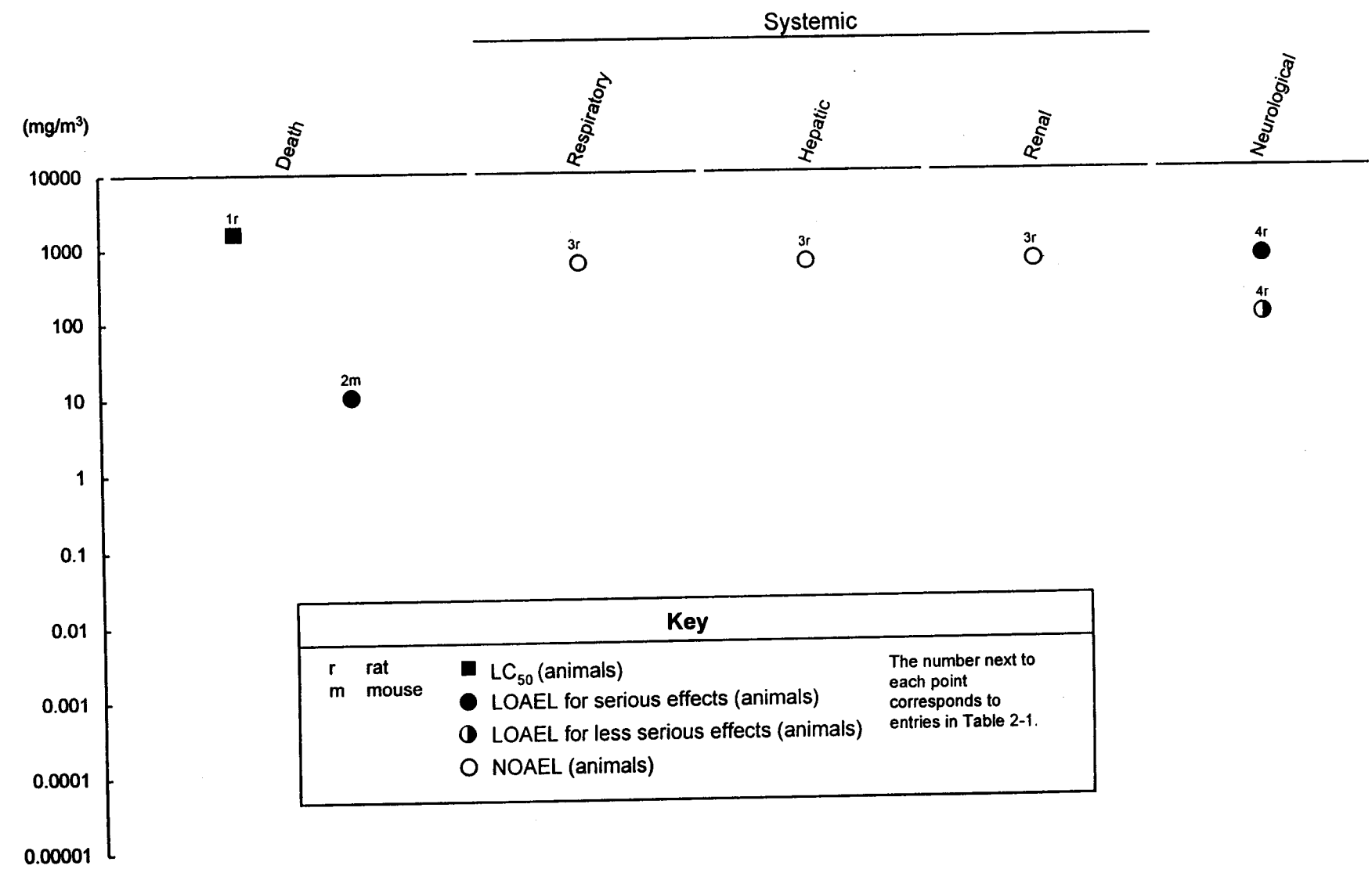
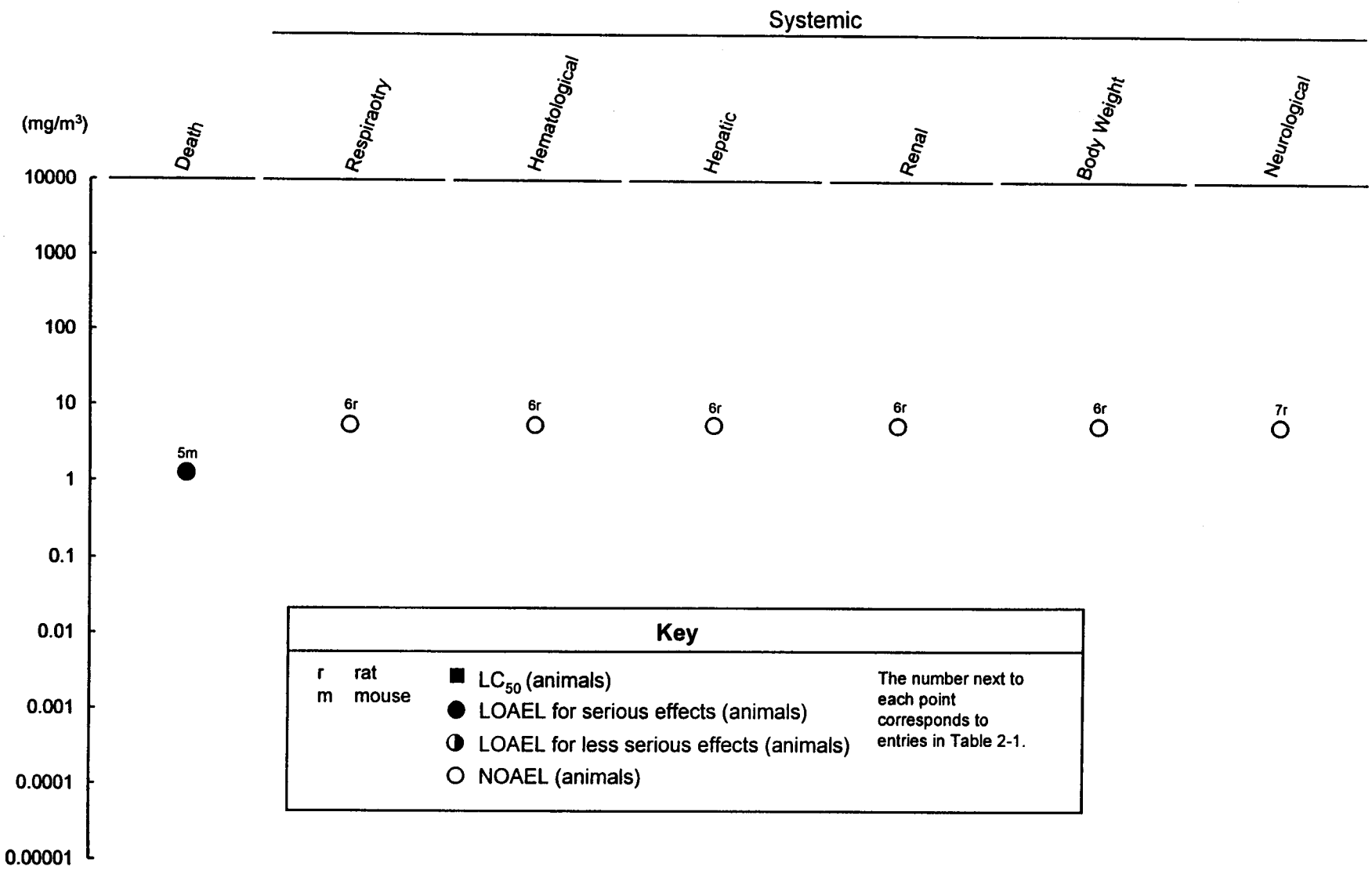


Figure 2-1. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Inhalation (cont.)

Intermediate (15-364 days)



Therefore, the estimated doses delivered to the animals cannot be precisely determined, and thus, the toxicity levels cited may be of questionable validity. In an intermediate-duration study with mice inhaling lindane dust aerosol in whole-body exposure chambers, 16% mortality was observed after 1 week of exposure to 10 mg/m^3, while exposures of up to 14 weeks resulted in 22% mortality at 5 mg/m^3, 2% mortality at 1 mg/m^3, and no mortality at 0.3 mg/m^3 (Klonne and Kintigh 1988).

2.2.1.2 Systemic Effects

Respiratory Effects. In humans, mucous membrane irritation of the nose and throat was observed after acute exposure to the HCH products dispensed by an overheated γ-HCH vaporizer (Conley 1952). Exposure levels were not reported and dermal exposure may also have occurred, although the observed irritation was probably due to direct action upon the mucous membranes.

No respiratory effects were observed in rats exposed to up to 603 mg/m^3 lindane aerosol for 4 hours (Oldiges et al. 1980). No respiratory effects were observed in rats exposed to lindane aerosol (up to 5 mg/m^3) for 90 days (Oldiges et al. 1983) or in mice similarly exposed for 14 weeks (Klonne and Kintigh 1988).

Cardiovascular Effects. Cardiovascular effects of HCH have been reported in humans exposed to HCH. Kashyap (1986) reported electrocardiogram (ECG) abnormalities in 15% of 45 factory workers involved in the production of technical-grade HCH; exposure concentrations were not reported and dermal exposure may have occurred.

No studies were located regarding cardiovascular effects in animals following inhalation exposure to HCH.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans or animals following inhalation exposure to HCH.

Hematological Effects. Hematological effects have been reported in humans following acute or chronic inhalation exposure to γ-HCH; however, a causal relationship between exposure to γ-HCH and hematological effects in humans has not been established. Hypochromic anemia was reported in a 2.5-year-old boy who was exposed to γ-HCH in a home in which a pesticide vaporizer was operated. Air γ-HCH concentrations measured in the basement and living room of the house were 2.4–5.5 $\mu g/m^3$; however, the actual concentration the child was exposed to and the duration of exposure were not determined (Morgan

et al. 1980). Aplastic anemia was reported in a boy exposed to γ-HCH used as an insecticide in his home and in a man exposed at work (Rugman and Cosstick 1990). The anemia was reversible and was not present in other family members. The levels and routes of exposure are not known, although they are presumed to be inhalation and dermal. Other hematological abnormalities, including isolated instances of leukopenia, leukocytosis, granulocytopenia, granulocytosis, eosinophilia, monocytosis, and thrombocytopenia, have been reported following chronic human occupational exposure to γ-HCH (Brassow et al. 1981; Jedlicka et al. 1958). Exposure concentrations were not specified in these studies and concomitant dermal exposure probably occurred. Although Brassow et al. (1981) reported slight changes in clinical chemistry tests in 60 human workers, there were no cases of severe impairment of health. Granulocytopenia, aplastic anemia, paramyeloblastic leukemia, and pancytopenia have been reported in a number of case reports of individuals following exposure to γ-HCH and other pesticides such as DDT in the home, during the handling of the pesticide, or from a nearby formulating plant (Danopoulos et al. 1953; Friberg and Martensson 1953; Gewin 1939; Loge 1965; Mendeloff and Smith 1955). Exposure concentrations were not reported, dermal exposure was likely, and in many cases there was concomitant exposure to other pesticides; therefore, determination of a causal relationship between exposure and hematological effects cannot be made.

No hematological effects were seen in rats exposed to lindane aerosol (up to 5 mg/m^3) for 90 days (Oldiges et al. 1983).

Hepatic Effects. In humans, statistically significant increases in the blood levels of the enzymes lactate dehydrogenase (33%), leucine aminopeptidase (45%), and γ-glutamyl transpeptidase (174%) were reported in 19 individuals occupationally exposed to technical-grade HCH for over 10 years in an HCH-formulating plant (Kashyap 1986); the HCH isomer concentrations showed a 1-fold increase compared to the control group of workers. Both inhalation and dermal exposure probably occurred. The large standard deviation (SD) from the mean reported for γ-glutamyl transpeptidase in exposed workers (mean±SD = 22.2±40.31 25 μ/mL) suggests the increased level of this enzyme may not be related to HCH exposure or that individual responses may vary.

No hepatic effects were observed in rats after acute exposure to 603 mg/m^3 γ-HCH (Oldiges et al. 1980). Rats exposed to lindane aerosol (5 mg/m^3) exhibited increased hepatic cytochrome P-450 concentration after 90 days, but this level returned to control values after a 4-week recovery period (Oldiges et al. 1983).

Renal Effects. No studies were located regarding renal effects in humans following inhalation exposure to HCH.

No renal effects were seen in rats exposed to up to 603 mg/m^3 lindane aerosol for 4 hours (Oldiges et al. 1980) or up to 5 mg/m^3 lindane aerosol for 90 days (Oldiges et al. 1983).

Endocrine Effects. Serum luteinizing hormone levels which were reported to be statistically significant, increased in 54 men occupationally exposed to γ-HCH for approximately 8 years in a γ-HCH producing factory (Tomczak et al. 1981). The mean serum concentration of follicle stimulating hormone was increased and testosterone was decreased; but these differences were not statistically significant (Tomczak et al. 1981).

No studies were located regarding endocrine effects in animals following inhalation exposure to HCH.

Dermal Effects. No studies were located regarding dermal effects in humans or animals following inhalation exposure to HCH.

Ocular Effects. No studies were located regarding ocular effects in humans following inhalation exposure to HCH.

Mice exposed to lindane aerosol (up to 5 mg/m^3) for 14 weeks exhibited no ophthalmic effects (Klonne and Kintigh 1988).

Body Weight Effects. No studies were located regarding body weight effects in humans following inhalation exposure to HCH.

No body weight effects were seen in rats exposed to up to 5 mg/m^3 lindane aerosol for 90 days (Oldiges et al. 1983).

2.2.1.3 Immunological and Lymphoreticular Effects

A statistically significant increase (approximately 18%) in the level of immunoglobulin M (IgM) was noted in 19 workers occupationally exposed to technical-grade HCH during pesticide formulation as compared to 14 nonexposed workers (Kashyap 1986). The HCH isomer concentrations in serum showed a 10-fold

increase when compared to the control group. Both inhalation and dermal exposure probably occurred, and the measurement of IgM alone is not a reliable measure of immune function in adults.

No studies were located regarding immunological or lymphoreticular effects in animals following inhalation exposure to HCH.

2.2.1.4 Neurological Effects

Paresthesia of the face and extremities, headache, and vertigo have been reported in a group of 45 workers occupationally exposed during manufacture and formulation of technical-grade HCH for several years (Kashyap 1986); exposure concentrations were not reported. Both inhalation and dermal exposure probably occurred. Abnormal electroencephalographic (EEG) patterns (increased variation in the frequency and amplitude of wave pattern or more serious changes without specific EEG signs) have been reported in 16 of 37 workers following exposure to γ-HCH for 0.5–2 years in a fertilizer plant (Czegledi-Janko and Avar 1970). Exposure concentrations were not reported; however, these EEG changes were found to correlate with blood levels of γ-HCH. Weakness of the left and right limbs, dysarthria, and dysphagia were seen in an agricultural worker exposed by inhalation and dermal contact to unspecified levels of several organochlorine pesticides, including lindane (Fonseca et al. 1993).

Rats exposed to various concentrations of 99.6% lindane aerosol via nose-only inhalation for 4 hours exhibited dose-related neurological effects when observed for up to 22 days after exposure (Ullmann 1986b). Slight-to-moderate sedation was observed after exposure to 101 mg/m^3; slight-to-severe sedation was noted after exposure to 378 mg/m^3; restlessness, excitation, and ataxia were seen after exposure to 642 and 2,104 mg/m^3; and spasms were also noted at the highest concentration (2,104 mg/m^3). Rats exposed to 0.02–5 mg/m^3 lindane aerosol for 90 days exhibited a "slightly disturbed general condition" beginning at day 15 (Oldiges et al. 1983). Mice were similarly exposed for 14 weeks and exhibited no clinical signs of neurotoxicity (Klonne and Kintigh 1988).

2.2.1.5 Reproductive Effects

Statistically significant increases in the levels of serum luteinizing hormone were reported in a group of 54 men occupationally exposed to γ-HCH for approximately 8 years in a γ-HCH-producing factory (Tomczak et al. 1981). Although the mean serum concentration of follicle stimulating hormone was

increased and testosterone was decreased, these differences were not statistically significant. No causal relationship could be established because exposure levels were not reported. These hormonal changes may have resulted in diminished reproductive capability.

No studies were located regarding reproductive effects in animals following inhalation exposure to HCH.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following inhalation exposure to HCH.

2.2.1.7 Genotoxic Effects

No increase in the frequency of chromosome aberrations was observed in humans exposed primarily to γ-HCH by inhalation in a pesticide production factory (Kiraly et al. 1979). These individuals had been exposed for 8 hours/day for at least 6 months. Other studies are available regarding genotoxic effects in humans exposed to a wide variety of pesticides, including lindane, when they were used on farms (Rupa et al. 1988, 1989a, 1989b, 1989c). The specific effects of HCH, apart from the effects due to the other exposures, are not known.

No studies were located regarding genotoxic effects in animals following inhalation exposure to HCH.

Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

Use of γ-HCH pesticides by farmers in 4 western or midwestern states was associated with a 50% increased risk of having non-Hodgkin's lymphoma (Blair et al. 1998). There was some evidence of a nonstatistically significant dose-response relationship because odds ratios (OR) were greater in farmers who used γ-HCH pesticides $20 compared with <20 years prior to diagnosis (OR 1.7 compared with 1.3) and $5 compared with <5 times per year (OR 2.0 versus 1.6). However, use of certain insecticides such as 2,4-D and diazinon reduced odds ratios from 1.5 to 1.2 and 1.3, respectively. The authors concluded that γ-HCH is not a major factor in the development of non-Hodgkin's lymphoma but may play some role.

No studies were located regarding carcinogenic effects in animals following inhalation exposure to HCH.

2.2.2 Oral Exposure

There are two tables and two figures for the Levels of Significant Exposure for oral exposure to the HCH isomers. Table 2-2 and Figure 2-2 are for γ-HCH. Table 2-3 and Figure 2-3 are for α-, β-, and δ-HCH, and technical-grade HCH.

2.2.2.1 Death

Occasional deaths of humans (usually children) have been reported following ingestion of γ-HCH, often from the tablets intended for γ-HCH vaporizers (Storen 1955). γ-HCH has also been used for suicide (Sunder Ram Rao et al. 1988). The levels associated with death are not known.

γ-HCH has been shown to be lethal to animals following single gavage administration (Gaines 1960; Liu and Morgan 1986; Tusell et al. 1987). The LD_{50} value for female rats is 91 mg/kg, and the LD_{50} value for male rats is 88 mg/kg (Gaines 1960). One of 7 male Wistar rats died following a single oral administration of 60 mg/kg γ-HCH (Martinez et al. 1991). DBA/2 strain mice, recognized as being "unresponsive" to microsomal enzyme induction, are more sensitive to the acute lethal effects of γ-HCH than C57BL/6 strain mice when exposed to 20 mg/kg/day for 10 days (Liu and Morgan 1986). In a 15-week study, 2 of 12 F-344 rats treated with 20 mg/kg/day died (Chadwick et al. 1988). A 2-year study in rats fed lindane in their diets (32 mg/kg/day) also found a significantly increased mortality rate compared with controls (Amyes 1990). The oral LD_{50} for technical-grade HCH in CFT-Wistar rats treated once by gavage was 2,428 mg/kg (Joseph et al. 1992a). Exposure to 5 mg/kg/day of technical-grade HCH for 90 days resulted in the deaths of 6/12 male rats and 4/12 female rats (Dikshith et al. 1991b). Exposure to low levels (0.4 mg/kg/day) of technical-grade HCH in the diet for 360 days resulted in deaths of 4/20 rats (Dikshith et al. 1991a). However, the deaths occurred late in the study and were accompanied by other changes indicating that they were due to pathogenic infection rather than HCH exposure.

The LD_{50} for rats and the LOAEL values from the intermediate-duration studies are recorded in Tables 2-2 and 2-3 and plotted in Figures 2-2 and 2-3.

TABLE 2-2. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Oral

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
ACUTE EXPOSURE							
Death							
1	Rat (Sherman)	once (GO)				88 M (LD_{50}) 91 F (LD_{50})	Gaines 1960
2	Rat (Wistar)	once (GO)				60 M (1/7 deaths)	Martinez et al. 1991
Systemic							
3	Rat	2wks (F)	Hepatic		72 Altered activities of serum aminotransferases, alkaline phosphatase, decreased soluble enzymes and altered carbohydrate metabolism.		Srinivasan and Radhakrishnamurty 1988
4	Rat (Wistar)	14 d ad libitum (F)	Renal			72 M (10% increase in kidney weight, altered excretion patterns, distention of glomeruli, swelling of tubular epithelia)	Srinivasan et al. 1984

TABLE 2-2. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
5	Mouse (B6C3F1)	3 d 1x/d (GO)	Resp	40 M			Hong and Boorman 1993
			Cardio	40 M			
			Gastro	40 M			
			Hemato		20M (Transient reduction in marrow progenitor cell number)		
			Hepatic	40 M			
			Renal	40 M			
			Endocr	40 M			
			Bd Wt	40 M			
6	Mouse (B6C3F1)	10 d 1 x/d (GO)	Resp	20 M			Hong and Boorman 1993
			Cardio	20 M			
			Gastro	20 M			
			Hemato		10M (Transient decrease in marrow progenitor cell numbers)		
			Hepatic	20 M			
			Renal	20 M			
			Bd Wt	20 M			
Immunological/Lymphoreticular							
7	Mouse (B6C3F1)				10M (Dose-related decrease in thymus and spleen weights)		Hong and Boorman 1993
8	Mouse (B6C3F1)	3 d 1x/d (GO)		10 M	20M Decreased thymus transient weight	40 M Atrophy of thymus cortex	Hong and Boorman 1993

TABLE 2-2. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
Neurological							
9	Rat (Sprague-Dawley)	6 d 1x/d (GO)			3M (increased pineal *N*-acetyltransferase, decreased serotonin levels)		Attia et al. 1991
10	Rat (Wistar)	once (GO)				30 M (convulsions, decreased calmodulin mRNA expression in the brain)	Barron et al. 1995a
11	Rat (Long- Evans)	once (GO)			5M (myoclonic jerks and single clonic seizure in kindled animals)	10 M (myoclonic jerks and single clonic seizures in naive animals)	Gilbert and Mack 1995
12	Rat (Sprague-Dawley)	4 d 1x/d (GO)		1[b] M	3M (increased kindling acquisition)	10 M (seizures)	Joy et al. 1982
13	Rat (Wistar)	once (GO)				60 (convulsions)	Martinez and Martinez-Conde 1995
14	Rat (Wistar)	once (GO)				60 M (tonic-clonic seizures)	Martinez et al. 1991
15	Rat (Wistar)	3 d 1x/d (GO)			5 (decreased myelin and 2',3'-cyclic nucleotide 3'-phosphodiesterase activity in brains)		Serrano et al. 1990a

TABLE 2-2. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
16	Rat (Wistar)	once (GO)		15 M		20 M (convulsions)	Vendrell et al. 1992a
17	Rat (Sprague-Dawley)	once (GO)				30 M (seizures)	Wooley and Griffith 1989
	Reproductive						
18	Rat	6 days, day 9-14 of lactation			1M (reduced testosterone level at puberty, relative testes weight)		Dalsenter et al. 1997a
19	Rat	once day 9 or 14 of lactation (GO)			6M Reduced relative testical and epidymis weight (~10%), spermatid and sperm counts (~8-10%), testosterone levels (~30-50%), Leydig cell numbers and spermatogenisis.		Dalsenter et al. 1997a
20	Rat (Long- Evans)	7 d 1x/d (GO)		40 F			Laws et al. 1994
21	Rat (CDF-F344)	once			25 (increased length of estrous cycle)		Uphouse and Williams 1989

TABLE 2-2. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL	LOAEL Less serious	LOAEL Serious	Reference
Developmental							
22	Rat (Wistar)	single dose day 15 of gestation (GO)			30 (reduction of serum testosterone concentration in adult offspring)		Dalsenter et al. 1997b
23	Rat (Wistar)	Gd 6-15 1x/d (GO)		25 F			Khera et al. 1979
24	Rat (CFY)	Gd 6-15 1x/d (G)		20 F			Palmer et al. 1978a
25	Rat (Wistar)	once (GO)			20 (regional changes in brain noradrenaline and serotonin levels in suckling rats)		Rivera et al. 1991
26	Mouse DBA/2J	Single oral dose on day 12 of gestation GI			45 (decrease in fetal and placental weight)		Hassoun and Stohs, 1996a
27	Mouse C57BL/6N	Single oral dose on day 12 of gestation GI			30 (decrease in fetal weight, fetal thymus weight)		Hassoun and Stohs, 1996a

TABLE 2-2. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
28	Rabbit (New Zealand)	Gd 6-18 1x/d (G)		20 F			Palmer et al. 1978a
INTERMEDIATE EXPOSURE							
Death							
29	Rat (Fischer-344)	15 wk 1x/d (GO)				20 F (2/12 deaths)	Chadwick et al. 1988
Systemic							
30	Rat (Wistar)	15 d ad libitum (F)	Hepatic		1.8 M Increases in lipid peroxidation, level of cytochrome P-450, and activities of superoxide dismutase.		Barros et al. 1991
31	Rat (Wistar)	30 d ad libitum (F)	Hepatic		1.8 M Increases in lipid peroxidation, level of cytochrome P-450, and activities of superoxide dismutase.		Barros et al. 1991
32	Rat (Wistar)	40d (F)	Hepatic Renal	50	 5		Desi 1974

TABLE 2-2. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL	LOAEL Less serious	LOAEL Serious	Reference
33	Rat (Wistar)	7 and 15 days gavage (SC)	Gastro		20 Reduction in jejunum maltase activity		Moreno et al. 1996
34	Rat (Wistar)	12 wk ad libitum (F)	Hepatic	0.4	2 (centrilobular hypertrophy)		Suter 1983
			Renal	0.4	2 (ddtubular distension, basophilic tubules)		
			Hemato	10			
35	Mouse (dd)	24 wk ad libitum (F)	Hepatic		90M (centrilobular hypertrophy)		Ito et al. 1973
Immunological/Lymphoreticular							
36	Mouse (Swiss albino)	24 wk ad libitum (F)			0.012[c] F (biphasic changes in cell- and humoral-mediated immune system)	1.2 F (necrosis of thymus)	Meera et al. 1992
Neurological							
37	Rat (Wistar)	90 d ad libitum (F)				90 M (tonic convulsions)	Arisi et al. 1994
38	Rat (Long- Evans)	30 d 1x/d (GO)				10 M (myoclonic jerks and clonic seizures)	Gilbert 1995

TABLE 2-2. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
39	Rat (Long- Evans)	10 wk 3 d/wk (GO)				10 M (myoclonic jerks and clonic seizures)	Gilbert 1995
40	Rat (Wistar)	30 d (GO)			2 (decreased dopamine levels)		Martinez and Martinez-Conde 1995
41	Rat (Wistar)	30 d ad libitum (F)		12.3 M	25.4 M (reduced tail nerve conduction velocity)		Muller et al. 1981
	Reproductive						
42	Rat (Fischer-344)	15 wk 1x/d (GO)		5 F	10 F (disrupted ovarian cycling, antiestrogenic effects)		Chadwick et al. 1988
43	Rabbit (hybrid)	12 wk 3 d/wk (GO)			0.8 F (reduced ovulation rate)		Lindenau et al. 1994
44	Rabbit (New Zealand)	12-15 wk 3 d/wk (GO)		0.8 F			Seiler et al. 1994

TABLE 2-2. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
Developmental							
45	Rat (Wistar)	21 day GO 21 GD and 28 LD or 28 LD (F)			25 Increased liver weight and decreased kidney weight in pups exposed during gestatino and lactation		Srinivasan et al. 1991a
46	Rabbit (New Zealand)	12-15 wk 3 d/wk (GO)		0.8 F			Seiler et al. 1994
CHRONIC EXPOSURE							
Death							
47	Rat (Wistar)	up to 52 weeks ad libitum (F)				32 F (increased mortality rate)	Amyes et al. 1990
Systemic							
48	Rat (Wistar)	5 to 52 weeks ad libitum (F)	Hepatic Renal	0.7 M 0.8 F 0.7 M 8 F	7 M (periacinar hepatocytic 8 F hypertrophy) 7 M (male: pale kidneys, 28 F increased kidney weight, urinary volume, and protein, tubular necrosis. female: increase in urine specific gravity, urea, and creatinine and kidney weight)		Amyes et al. 1990

TABLE 2-2. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
49	Rat (Wistar)	109 weeks (F)	Hepatic	3.5 M 4.0 F		7 M (focal necrosis, fatty 8 F degeneration, 35% increase in liver weight)	Fitzhugh et al. 1950
			Renal	3.5 M 4 F	7 M (focal nephritis) 8 F		
			Bd Wt	56 M	112M (17% decrease in body weight gain)		
				64 F	128F (13 % decrease in body weight gain)		
Cancer							
50	Mouse (B6C3F1)	80 wk ad libitum (F)				13.6 M (CEL: hepatocellular carcinoma)	NCI 1977
51	Mouse (F-1 hybrid)	24 mo ad libitum (F)				27.2 F (CEL: hepatocellular carcinoma, lung tumors)	Wolff et al. 1987

[a]The number corresponds to entries in Figure 2-2.

[b]Used to derive an acute-duration oral Minimal Risk Level (MRL) of 0.01 mg/kg/day for gamma-HCH; 1 mg/kg/day divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, 10 for human variability) = 0.01 mg/kg/day.

[c]Used to derive an intermediate-duration oral Minimal Risk Level (MRL) of 0.00001 mg/kg/day for gamma-HCH; 0.012 mg/kg/day divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, 10 for human variability) = 0.00001 mg/kg/day.

Bd Wt = body weight; CEL = cancer effect level; d = day(s); F = female; (F) = food; (G) = gavage; (GO) = gavage, oil; (GO) = gavage, water; Gd = gestation day(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mRNA = messenger ribonucleic acid; mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; wk = week(s); x = time(s); yr = year(s).

Figure 2-2. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Oral

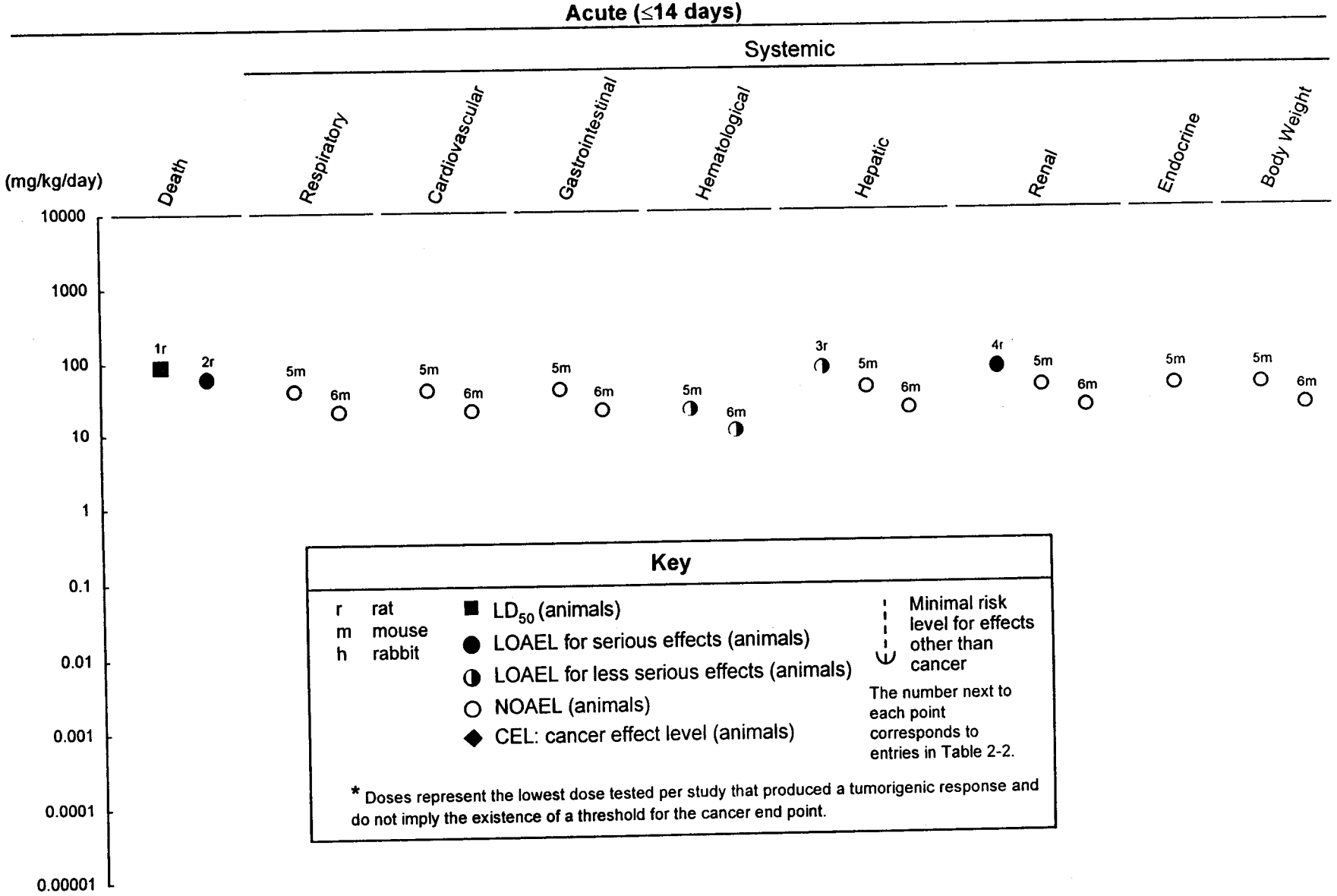


Figure 2-2. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Oral (cont.)

Acute (≤14 days)

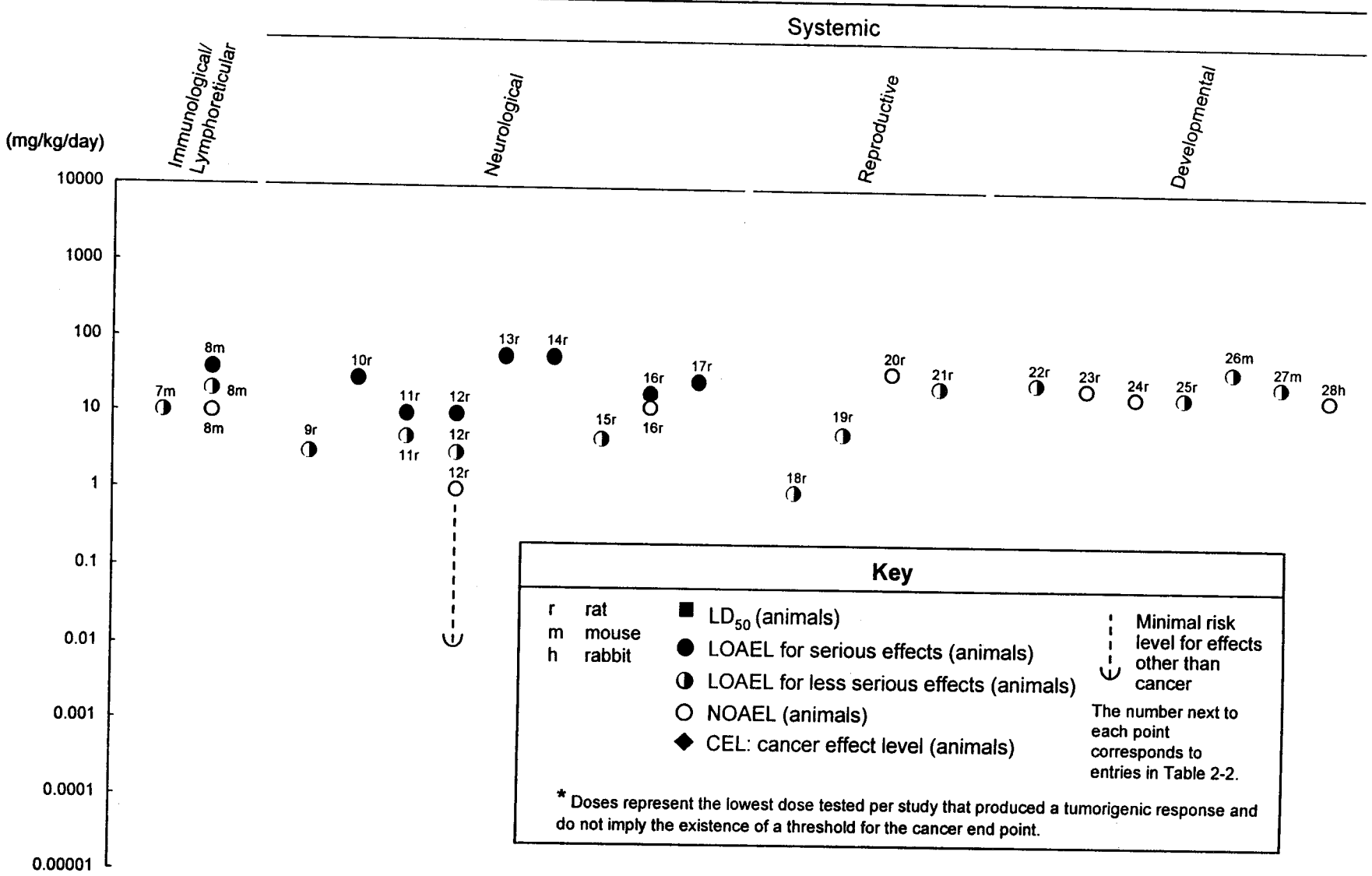


Figure 2-2. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Oral (cont.)

Intermediate (15-364 days)

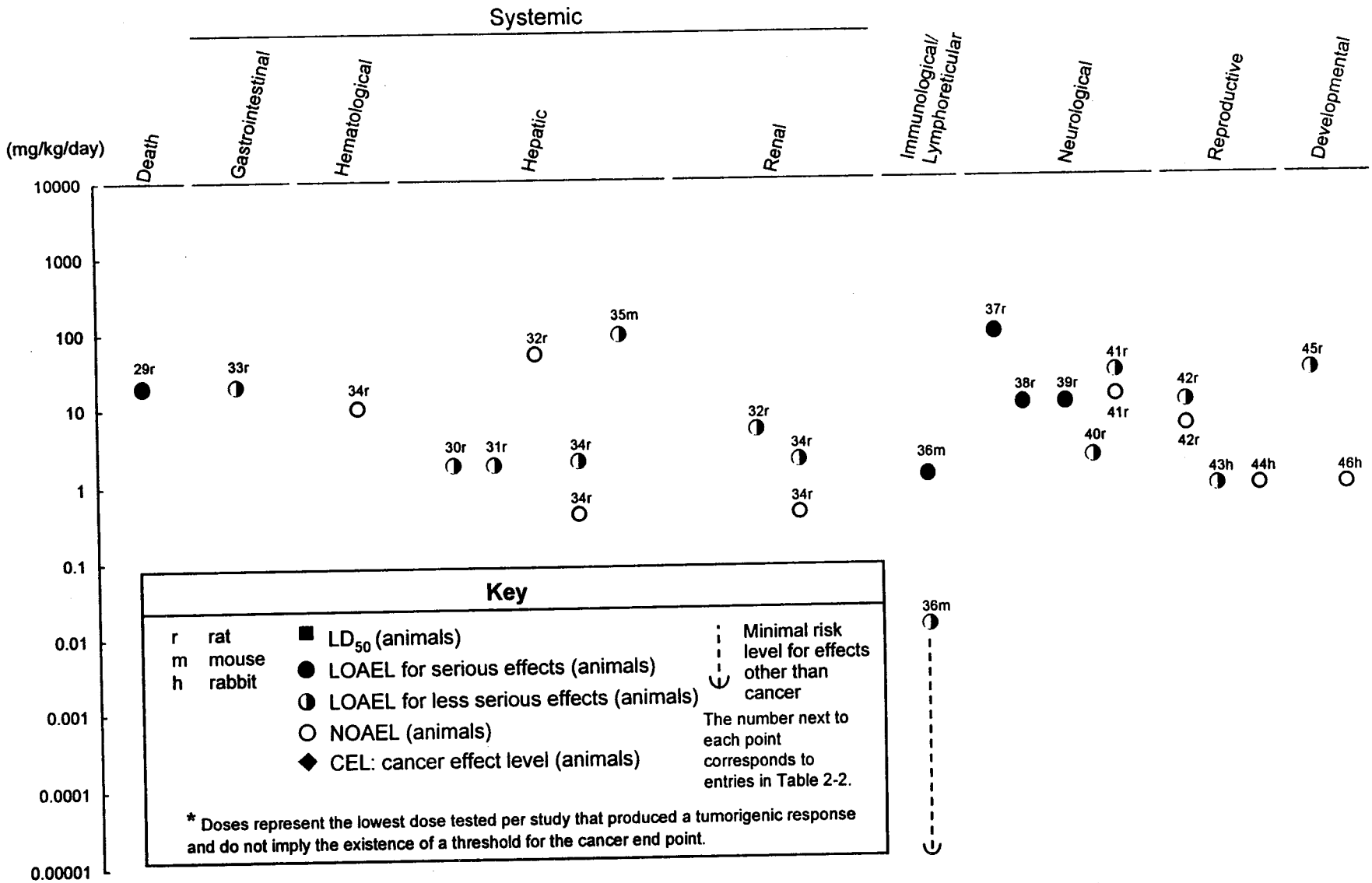


Figure 2-2. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Oral (cont.)

Chronic (≥365 days)

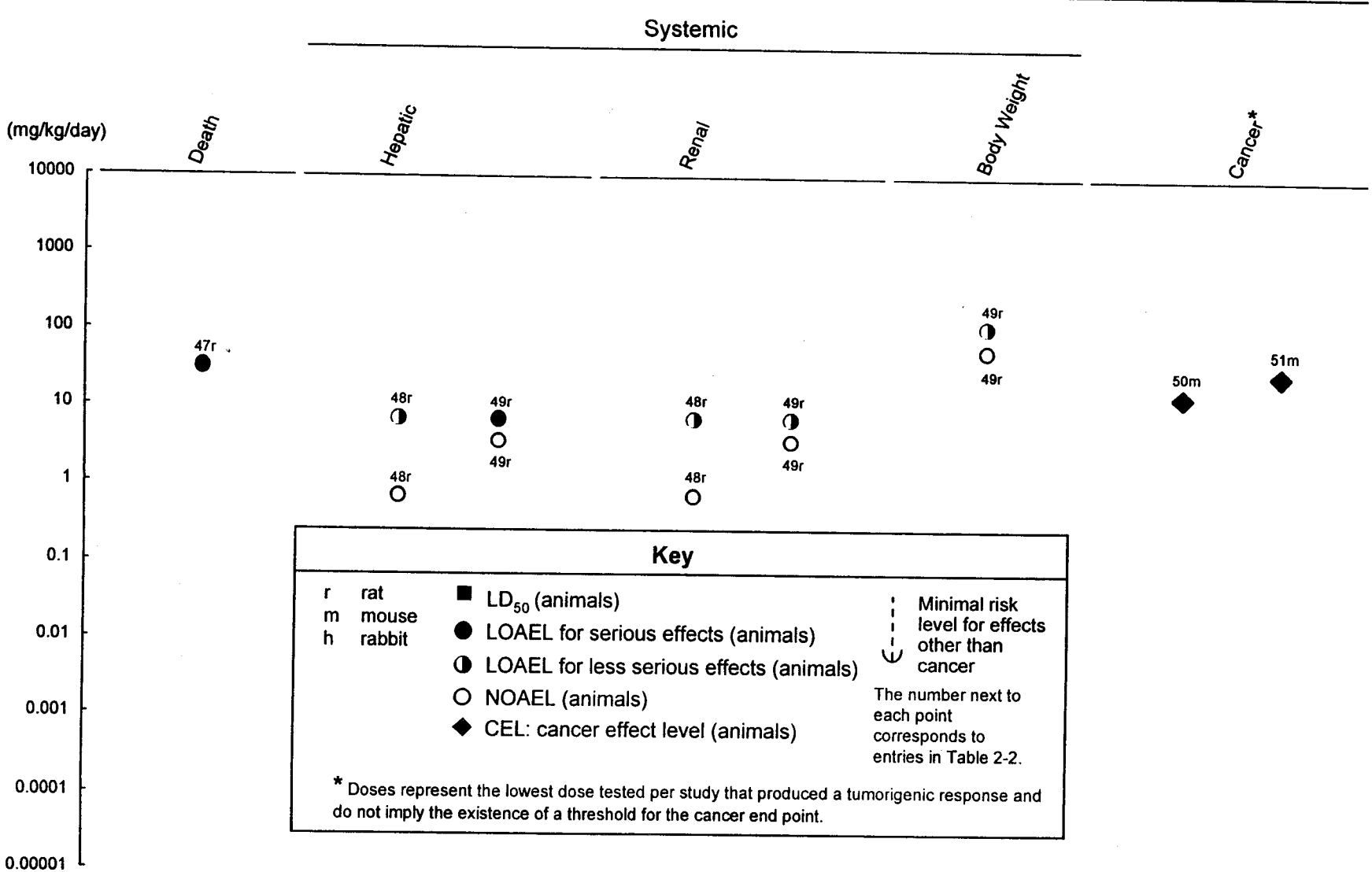


TABLE 2-3. Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Technical-Grade Hexachlorocyclohexane - Oral

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference/ Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Death							
1	Rat (CFT-Wistar)	once (GO)				2428 M (LD_{50})	Joseph et al. 1992a technical
Systemic							
2	Rat (NS)	once (GO)	Metab		100F (increased phosphoinositide turnover in erythrocyte membranes)		Agrawal et al. 1995 technical
3	Rat (Sprague-Dawley)	2 wk ad libitum (F)	Hepatic		90M (increased triglycerides, phospholipids and cholesterol, increased cytochrome C reductase and decreased glutathione peroxidase)		Ikegami et al. 1991a beta
4	Rat (Sprague-Dawley)	2 wk ad libitum (F)	Hepatic		90M (increased relative liver weight and cytochrome P-450 levels and decreased hepatic vitamin A levels)		Ikegami et al. 1991b beta
5	Rat (Wistar)	14 d ad libitum (F)	Renal			72 M (tubular degeneration, distention of glomeruli, swelling of tubular epithelia, 22% increase in kidney weight, altered excretion patterns)	Srinivasan et al. 1984 beta

TABLE 2-3. Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Technical-Grade Hexachlorocyclohexane - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ Chemical Form
6	Mouse (Swiss albino)	Gd 9 once (GO)	Hepatic		5F (significantly decreased GOT, GPT, and lactate dehydrogenase (LD) activities)		Dikshith et al. 1990 technical
7	Mouse (NS)	1, 5, 15 d 1x/d (GO)	Hepatic			50 (congestion of portal vessels and central vein, fatty changes, granular degeneration)	Philip et al. 1989 technical
			Renal			50 (congestion of portal vessels and glomeruli, fatty changes, interstitial hemorrhaging)	
8	Mouse (Swiss albino)	2 wk ad libitum (F)	Hepatic		72M (226% increase in liver weight, increased serum alanine and aspartate aminotransferases and ALP, increased hepatic phosphatases and acid cathepsin)		Ravinder et al. 1989 technical
9	Mouse (Swiss albino)	2 wk ad libitum (F)	Hepatic		72M (cellular hypertrophy, centrilobular degeneration, focal necrosis)		Ravinder et al. 1990 technical
Neurological							
10	Rat (Wistar)	once (GO)			100M (decreased calmodulin mRNA expression in the brain)		Barron et al. 1995 delta
11	Mouse (B6C3F1)	1 wk ad libitum (F)		19[b] F	57F (ataxia)	190 F (lateral recumbancy)	Cornacoff et al. 1988 beta

TABLE 2-3. Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Technical-Grade Hexachlorocyclohexane - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ Chemical Form
Reproductive							
12	Mouse (Swiss albino)	Gd 9 once (GO)		5 F		25 F (increased fetal resorptions)	Dikshith et al. 1990 technical
INTERMEDIATE EXPOSURE							
Death							
13	Rat (NS)	360 d ad libitum (F)				0.4 M (4/20 deaths)	Dikshith et al. 1991a technical
14	Rat (NS)	90 d 1x/d (GO)				5 (6/12 M, 4/12 F died)	Dikshith et al. 1991b technical
Systemic							
15	Rat (NS)	3-6 mo 5 d/wk (GO)	Metab		5F (increased phosphoinositide turnover in erythrocyte membranes and cerebrum)		Agrawal et al. 1995 technical
16	Rat (Wistar)	30 d ad libitum (F)	Hepatic		1.8 M (increased cytochrome P-450 level, superoxide dismutase, catalase, NADPH-cytochrome P-450 reductase activities, and lipid peroxidation)		Barros et al. 1991 alpha

TABLE 2-3. Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Technical-Grade Hexachlorocyclohexane - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference/ Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
17	Rat (Wistar)	15 d ad libitum (F)	Hepatic		1.8 M (increased cytochrome P-450 level, superoxide dismutase, catalase, and lipid peroxidation activities)		Barros et al. 1991 alpha
18	Rat (NS)	30 d 1x/d (GO)	Hemato	60 M			Dikshith et al. 1989a technical
			Hepatic		60 M (decreased GOT and LDH activities, increased ALP activity, 65% increase in liver weight)		
			Renal	60 M			
19	Rat (NS)	360 d ad libitum (F)	Hepatic	0.4 M	2 M (increased liver weight)	20 M (focal necrosis, enlargement of hepatocytes, nuclear pyknosis, vacuolation, margination)	Dikshith et al. 1991a technical
			Renal	2 M		20 M (tubular necrosis, glomerular degeneration)	
20	Rat (NS)	90 d 1x/d (GO)	Hepatic		5 M (decreased liver and serum GOT and alkaline phosphatase activities)		Dikshith et al. 1991b technical
21	Rat (Charles Foster)	180 d 1x/d (GO)	Bd Wt		3 M (17% decrease in body weight gain)		Gautam et al. 1989 technical

TABLE 2-3. Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Technical-Grade Hexachlorocyclohexane - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ Chemical Form
22	Rat (CFT-Wistar)	7 wk ad libitum (F)	Hepatic		90M (decreased hepatic vitamin A content, GOT, GPT ALP, and beta-GLR activities, 121% increase in liver weight)		Joseph et al. 1992b technical
			Bd Wt		90M (17% decrease in body weight gain)		
23	Rat (CFT-Wistar)	7 wk ad libitum (F)	Hemato		90M (decreased white blood cell counts)		Joseph et al. 1992c technical
24	Rat (NS)	30 d 1x/d (GO)	Hepatic	50 M			Khanna et al. 1990 technical
			Renal	50 M			
25	Rat (Wistar)	90 d ad libitum (F)	Bd Wt		20F (significantly decreased body weight gain)		Nagaraja and Desiraju 1994 technical
26	Rat (Wistar)	13 wk ad libitum (F)	Hemato	4.5 M 5 F	22.5 M (decreased red blood 25 F cell, leukocyte, and hemoglobin concentrations)		Van Velsen et al. 1986 beta
			Hepatic		0.18[c] M (hyalinization of 0.2 F centrilobular cells)	4.5 M (hyalinization of 5 F centrilobular cells, focal cell necrosis, increased mitoses)	
			Renal	4.5 M	22.5 M (calcinosis in males)		
			Bd Wt	4.5 M 5 F	22.5 M (15% decrease in body 25 F weight)		
27	Mouse (dd)	32 wk ad libitum (F)	Hepatic	18 M 20 F	54 M (nuclear irregularities in 60 F foci of enlarged hepatocytes)		Hanada et al. 1973 beta

TABLE 2-3. Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Technical-Grade Hexachlorocyclohexane - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference/ Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
28	Mouse (dd)	24 wk ad libitum (F)	Hepatic		18M (centrilobular hypertrophy)		Ito et al. 1973 alpha
29	Mouse (dd)	24 wk ad libitum (F)	Hepatic		45M (centrilobular hypertrophy)		Ito et al. 1973 beta
30	Mouse (dd)	24 wk ad libitum (F)	Hepatic		90M (centrilobular hypertrophy)		Ito et al. 1973 delta
31	Mouse (Swiss)	2-8 mo ad libitum (F)	Hepatic		90 (100% increase in liver weight, decreased G6P and FDP activity, glycogen accumulation, smooth endoplasmic reticulum proliferation)		Karnik et al. 1981 technical
32	Mouse (HPB)	50 wk ad libitum (F)	Hepatic		90M (hyperplastic nodules)		Tryphonas and Iverson 1983 alpha
Immunological/Lymphoreticular							
33	Rat (Wistar)	13 wk ad libitum (F)				22.5 M (cortical atrophy in thymus) 25 F	Van Velsen et al. 1986 beta
34	Mouse (B6C3F1)	30 d ad libitum (F)		20 F	60F (decr. lymphoproliferative responses to T-cell mitogens, decr. natural killer cytolytic activity)		Cornacoff et al. 1988 beta

TABLE 2-3. Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Technical-Grade Hexachlorocyclohexane - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ Chemical Form
Neurological							
35	Rat (NS)	3 mo 6 d/wk 1x/d (GO)			50M (increased dopamine and decreased serotonin, acetylcholine, norepinephrine in cerebral cortex, behavioral changes, increased brain wave frequency)		Anand et al. 1991 technical
36	Rat (NS)	360 d 1x/d (F)		0.04 M		0.4 M (convulsions, tremors, hindlimb paralysis, salivation)	Dikshith et al. 1991a technical
37	Rat (NS)	120 d 1x/d (GO)			50M (increased motor activity, decreased resting stereotypic time)		Gopal et al. 1992 technical
38	Rat (Wistar)	30 d ad libitum (F)		106.2 M			Muller et al. 1981 alpha
39	Rat (Wistar)	30 d ad libitum (F)			66.3 M (reduced tail nerve conduction velocity)		Muller et al. 1981 beta
40	Rat (Wistar)	90 d ad libitum (F)			20F (increased GABA levels, increased GAD activity, decreased glutamate levels)		Nagaraja and Desiraju 1994 technical
41	Rat (Wistar)	13 wk ad libitum (F)		4.5 M 5 F		22.5 M (ataxia, coma) 25 F	Van Velsen et al. 1986 beta

TABLE 2-3. Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Technical-Grade Hexachlorocyclohexane - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ Chemical Form
Reproductive							
42	Rat (NS)	360 d 1x/d (F)		2 M		20 M (testicular degeneration)	Dikshith et al. 1991a technical
43	Rat (Charles Foster)	180 d 1x/d (GO)			3M (6% decrease in vas deferens weight, degeneration of inner muscle and cell layers)		Gautam et al. 1989 technical
44	Rat (CFT-Wistar)	7 wk ad libitum (F)				90 M (decreased testes, epididymides, and seminal vesicle weights, 30% decrease in sperm count)	Pius et al. 1990 technical
45	Rat (Charles Foster)	180 d 1x/d (GO)			3M (decreased seminiferous tubular and Leydig cell nuclear diameter)	6 M (seminiferous tubular degeneration)	Roy Chowdhury and Gautam 1990 technical
46	Rat (Wistar)	13 wk ad libitum (F)		0.9 M 0.2 F	4.5 M (decreased testes 1.0 F weight) (increased ovary weights)	22.5 M (atrophy of ovary and 25 F testes, hyperplastic and vacuolized endometrium epithelium in uterus)	Van Velsen et al. 1986 beta
47	Mouse (B6C3F1)	30 d ad libitum (F)		60 F			Cornacoff et al. 1988 beta
48	Mouse (Swiss)	3 mo ad libitum (F)				90 M (increased testis weight, degeneration of seminiferous tubules, decreased spermatocytes)	Nigam et al. 1979 technical

TABLE 2-3. Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Technical-Grade Hexachlorocyclohexane - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ Chemical Form
Developmental							
49	Rat (Wistar)	60 d ad libitum (G)			10F (alterations in levels of dopamine, serotonin, and noradrenaline in pup brains)		Nagaraja and Desiraju 1994 technical
50	Rat (Wistar)	21GD, 28 LD, 28 LD (F)			5 (increased liver weight in pups exposed during gestation and lactation)	20 (increased pup mortaility)	Srinivasan et al. 1991a beta
Cancer							
51	Rat (Wistar)	20 wk ad libitum (F)				2 F (CEL: increase in preneoplastic hepatic foci)	Schroter et al. 1987 alpha
52	Rat (Wistar)	20 wk ad libitum (F)				3 F (CEL: increase in preneoplastic hepatic foci)	Schroter et al. 1987 beta
53	Mouse (dd)	32 wk ad libitum (F)				18 M (CEL: hepatoma) 60 F	Hanada et al. 1973 alpha
54	Mouse (dd)	24 wk ad libitum (F)				45 M (CEL: hepatocellular carcinoma)	Ito et al. 1973 alpha
55	Mouse (DDY)	16-36 wk ad libitum (F)				90 M (CEL: hepatocellular carcinoma)	Ito et al. 1976 alpha
56	Mouse (Swiss)	2-4 mo ad libitum (F)	Hepatic			90 (CEL: liver tumors)	Karnik et al. 1981 technical

TABLE 2-3. Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Technical-Grade Hexachlorocyclohexane - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ Chemical Form
57	Mouse (DDY, ICR, DBA/2, C57BL/6, C3H/He)	24 wk ad libitum (F)				90 M (CEL: hepatocellular carcinoma) 100 F	Nagasaki et al. 1975b alpha
58	Mouse (Swiss)	2-8 mo ad libitum (F)				90 (CEL: hepatocellular carcinoma)	Thakore et al. 1981 technical
59	Mouse (HPB)	50 wk ad libitum (F)				90 M (CEL: hyperplastic nodules and adenomas in liver)	Tryphonas and Iverson 1983 alpha
60	Mouse (DD)	16-36 wk ad libitum (F)				90 M (CEL: hepatoma)	Tsukada et al. 1979 alpha
CHRONIC EXPOSURE							
Systemic							
61	Rat (Wistar)	107 weeks ad libitum (F)	Hepatic	0.7 M 0.8 d F	3.5 M (focal necrosis, fatty 4 F degeneration, 32% increase in liver weight)		Fitzhugh et al. 1950 alpha
			Renal	7 M 8 F	56 M (focal nephritis) 64 F		
			Bd Wt	7 M	56 M (18% decrease in body weight gain)		
				8 F	64 F (13% decrease in body weight gain)		

TABLE 2-3. Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Technical-Grade Hexachlorocyclohexane - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ Chemical Form
62	Rat (Wistar)	107 weeks ad libitum (F)	Hepatic		0.7 M (focal necrosis, fatty 0.8 F degeneration, 33% increase in liver weight)		Fitzhugh et al. 1950 beta
			Renal	7 M 8 F	56 M (focal nephritis) 64 F		
			Bd Wt	56 M 0.8 F	8F (12% decrease in body weight gain)		
63	Rat (Wistar)	107 weeks ad libitum (F)	Hepatic	0.7 M 0.8 F	3.5 M (very slight microscopic 4 F damage)	7 M (focal necrosis, fatty 8 F degeneration, 36% increase in liver weight)	Fitzhugh et al. 1950 technical
			Renal	7 M 8 F	56 M (focal nephritis) 64 F		
			Bd Wt	7 M 8 F	56 M (decreased body weight 64 F gain)		
Neurological							
64	Mouse (Swiss)	80 wk ad libitum (F)				17 (convulsions)	Kashyap et al. 1979 technical
65	Mouse (Swiss)	80 wk 1x/d (GO)				10 (convulsions)	Kashyap et al. 1979 technical
Cancer							
66	Rat	72 wk ad libitum (F)				50 (CEL: hepatocellular carcinoma)	Ito et al. 1975 alpha
67	Mouse (Swiss)	80 wk 1x/d (GO)				10 (CEL: hepatocellular carcinoma)	Kashyap et al. 1979 technical

TABLE 2-3. Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Technical-Grade Hexachlorocyclohexane - Oral (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL			Reference/ Chemical Form
					Less serious (mg/kg/day)		Serious (mg/kg/day)	
68	Mouse (Swiss)	80 wk ad libitum (F)					17 (CEL: hepatocellular carcinoma)	Kashyap et al. 1979 technical
69	Mouse (Swiss)	20 mo ad libitum (F)					21.3 M (CEL: hepatocellular carcinoma)	Munir et al. 1983 technical
70	Mouse (CF1)	104 wk ad libitum (F)					34 (CEL:hepatocellular carcinoma)	Thorpe and Walker 1973 beta

[a]The number corresponds to entries in Figure 2-3.
[b]Used to derive an acute-duration oral Minimal Risk Level (MRL) of 0.2 mg/kg/day for beta-HCH; 19 mg/kg/day divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, 10 for human variability) = 0.19 mg/kg/day.
[c]Used to derive an intermediate-duration oral Minimal Risk Level (MRL) of 0.0006 mg/kg/day for beta-HCH; 0.18 mg/kg/day divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, 10 for human variability) = 0.0006 mg/kg/day.
[d]Used to derive a chronic-duration oral Minimum Risk Level (MRL) of 0.008 mg/kg/day for alpha-HCH; 0.8 mg/kg/day divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, 10 for human variability) = 0.008 mg/kg/day.

ALP = alkaline phosphatase; Bd Wt = body weight; CEL = cancer effect level; d = day(s); F = female; FDP = fructose-1,6-diphosphatase; GABA = gamma-aminobutyric acid; GAD = glutamate decarboxylase; GLR = glucuronidase; GOT = glutamate oxaloacetate transaminase; G6P = glucose-6-phosphatase; GPT = glutamate pyruvate transaminase; Hemato = hematological; LD50 = lethal dose, 50% kill; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolism; mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s).

Figure 2-3. Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Technical-Grade Hexachlorocyclohexane - Oral

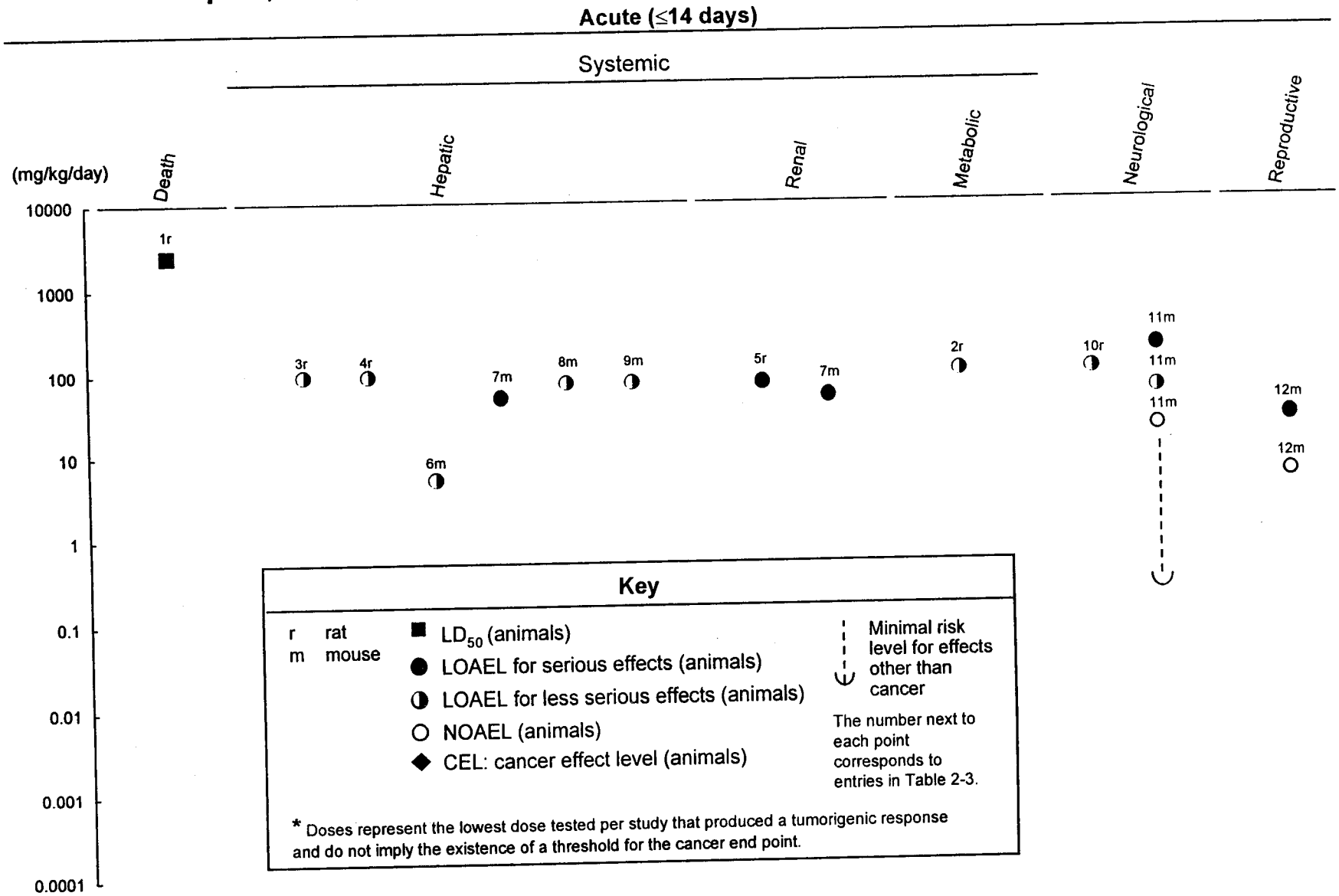


Figure 2-3. Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Technical-Grade Hexachlorocyclohexane - Oral (cont.)

Intermediate (15-364 days)

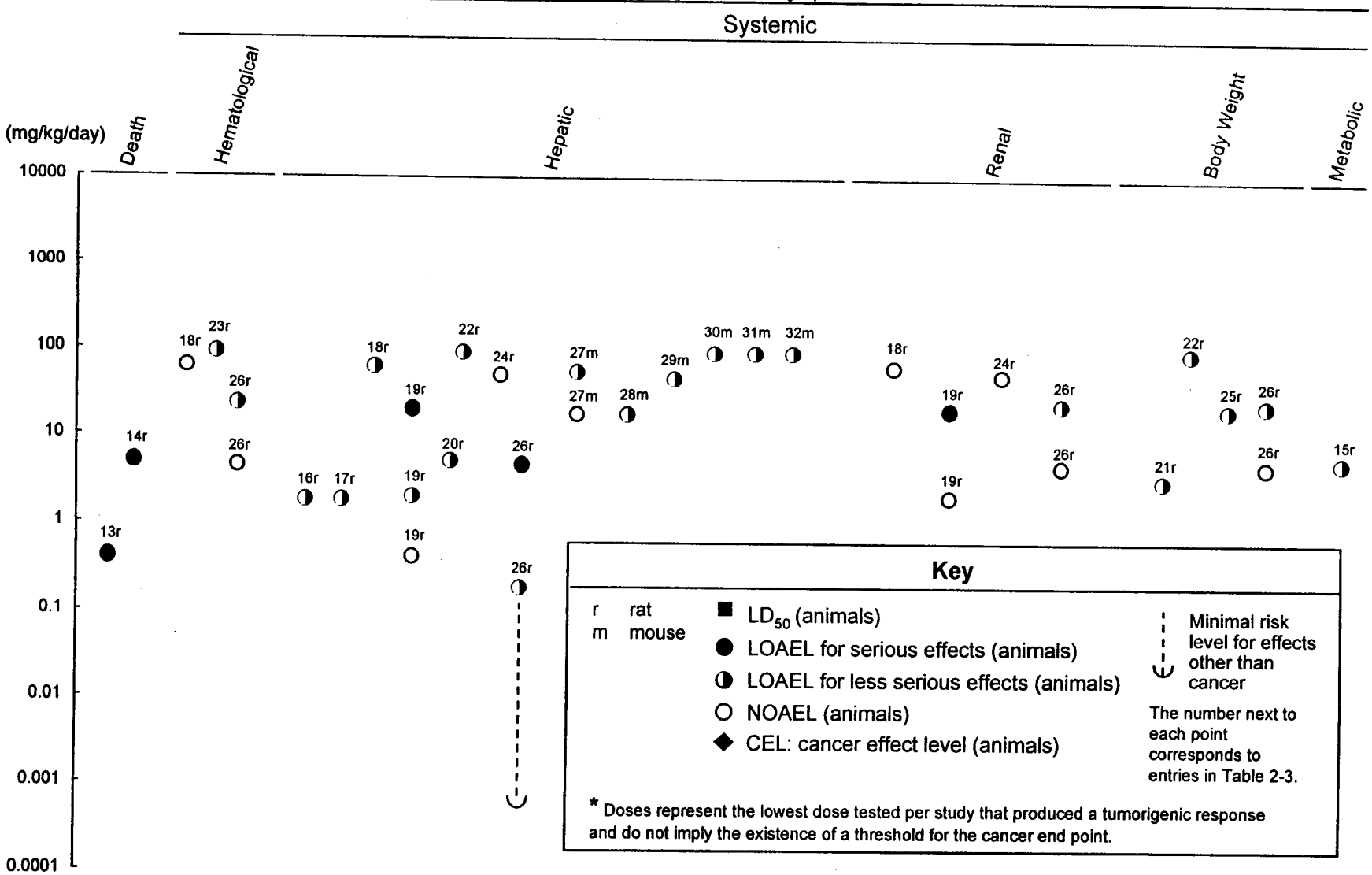


Figure 2-3. Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Technical-Grade Hexachlorocyclohexane - Oral (cont.)

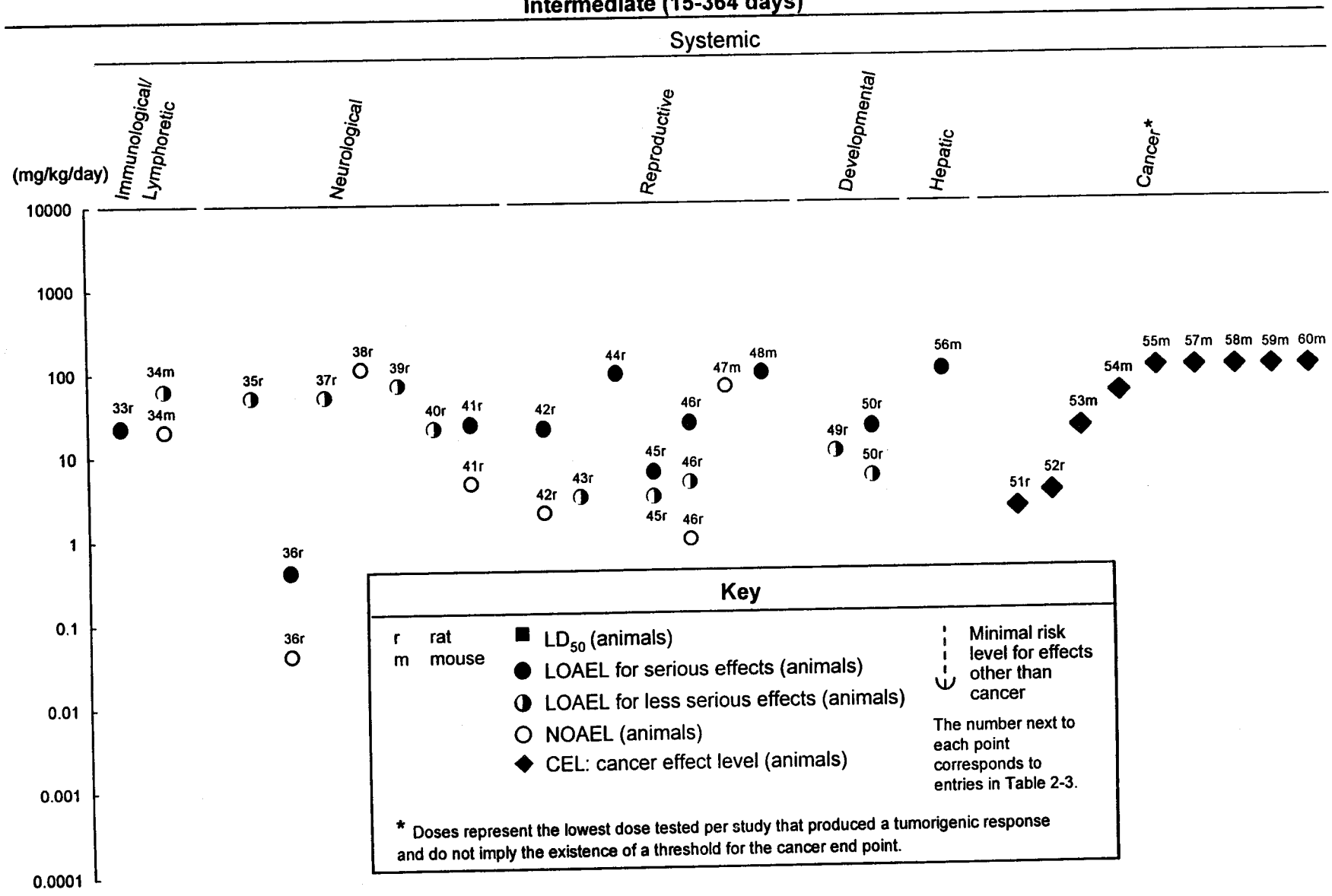
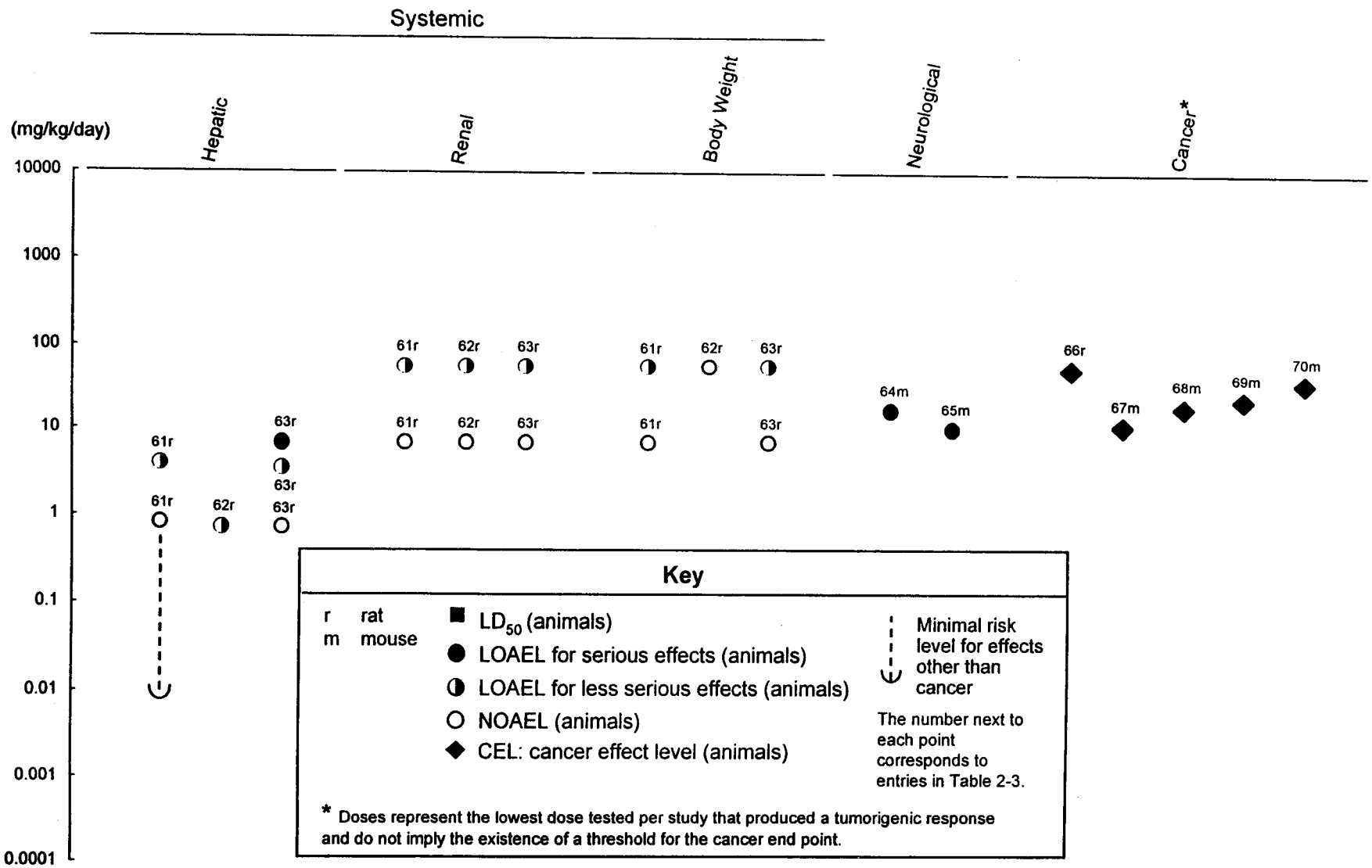


Figure 2-3. Levels of Significant Exposure to Alpha-, Beta-, Delta-, and Technical-Grade Hexachlorocyclohexane - Oral (cont.)

Chronic (≥365 days)



2.2.2.2 Systemic Effects

No studies were located regarding respiratory, dermal, or ocular effects in humans or animals following oral exposure to HCH. The animal studies in which systemic effects of HCH were examined, in most cases, used isomers of >99% purity. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Tables 2-2 and 2-3 and plotted in Figures 2-2 and 2-3.

Cardiovascular Effects. There are no reports of cardiovascular damage from γ-HCH or any other HCH isomer.

Gastrointestinal Effects. Decreased appetite, vomiting, nausea, and diarrhea have been observed in humans following ingestion of γ-HCH in contaminated food; exposure levels were not reported, but exposure was inferred from levels of γ-HCH measured in urine (Nantel et al. 1977). Vomiting and nausea are usual manifestations of lindane ingestion (Sunder Ram Rao et al. 1988).

The activities of the digestive enzyme maltase on brush border membrane of rat jejunum are reported to be inhibited by oral treatment with 20 mg/kg γ-HCH over 7 and 15 days (Moreno et al. 1996). In addition, γ-HCH has been shown to have an effect on intestinal functions such as uptake of glucose, glycine, and calcium in rats (Labana et al. 1997), and the effect depends on the nutritional status of the animals.

Hematological Effects. A woman who committed suicide by drinking γ-HCH was found to have disseminated intravascular coagulation during the period when serum γ-HCH levels were elevated (Sunder Ram Rao et al. 1988). No other reports were found on the possible effect of γ-HCH on blood-clotting factors in humans.

No hematological effects were noted in beagle dogs exposed to 12.5 mg γ-HCH/kg/day in the diet for 32 weeks or to 2.9 mg γ-HCH/kg/day in the diet for 104 weeks (Rivett et al. 1978). Twelve-week studies in rats, using lower doses (10 mg/kg/day), support this finding (Suter 1983). However, exposure to 22.5 mg β-HCH/kg/day in the diet for 13 weeks in rats was found to be more toxic, resulting in a statistically significant decrease in numbers of red blood cells and white blood cells and reduced hemoglobin and packed cell volume values (Van Velsen et al. 1986). Significant decreases in total white blood cell counts and

clotting time were reported in rats fed vitamin A-free diets containing technical-grade HCH at a dose level of 90 mg/kg/day for 7 weeks (Joseph et al. 1992c). In rats fed a vitamin A-supplemented diet containing the same dose level of technical-grade HCH, a significant reduction in total white blood cell count, but not red blood cell count, was observed (Joseph et al. 1992c). Significant suppression in bone marrow cellularity, erythrocyte precursors, and granulocyte-macrophage progenitor cells, and residual progenitor cell damage were reported in male $B6C3F_1$ mice given 20 or 40 mg γ-HCH/kg/day by gavage in corn oil for 3 days (Hong and Boorman 1993). Following 10 days of exposure to 10 or 20 mg γ-HCH/kg/day, dose-dependent decreases in bone marrow cellularity, granulocyte-macrophage progenitor cells, and pluripotent bone marrow stem cells were noted (Hong and Boorman 1993).

No hematological effects were seen in rats following oral exposure to 60 mg/kg/day technical-grade HCH for 30 days (Dikshith et al. 1989a).

Musculoskeletal Effects. In humans, ingestion of a single dose of approximately 15–30 mL γ-HCH powder was associated with seizures and limb muscle weakness and necrosis (Munk and Nantel 1977); a muscle biopsy was conducted on day 15 after ingestion and showed no evidence of denervation or neuropathy. Widespread striatal muscle necrosis was seen in a woman who died 11 days after intentionally ingesting 8 ounces of a 20% lindane solution (Sunder Ram Rao et al. 1988).

Decreased cross-sectional bone area was found in young rats treated with 20 mg/kg/day of γ-HCH by gavage for 10 weeks (Andrews and Gray 1990). Myelotoxicity, manifested as significant, dose-dependent decrease in marrow progenitor numbers, was seen in mice exposed to 10 or 20 mg/kg/day lindane for 10 days (Hong and Boorman 1993).

Hepatic Effects. No studies were located regarding hepatic effects in humans following oral exposure to HCH.

Significantly increased liver microsomal 7-ethoxycoumarin-o-dealkylase activity was found in Osborne-Mendel rats exposed to 11.2 mg γ-HCH/kg/day and in CF_1 and $B6C3F_1$ strain mice exposed to 23.6 and 50.5 mg/kg/day in the diet for 3 days (Oesch et al. 1982). No adverse effects were noted in rats exposed to 10 mg/kg/day for a minimum of 4 days (Joy et al. 1982). No significant increase in liver weight was reported, but no histopathological examinations were performed to confirm the presence or absence of toxicity. Hepatocellular damage as indicated by elevation in serum aminotransferases and decrease in hepatic

soluble enzymes was found in rats given 72 mg/kg/day γ-HCH for 2 weeks (Srinivasan and Radhakrishnamurty 1988). Significant increases in hepatic microsomal cytochrome P-450 levels and increases in hepatic microsomal superoxide anion production and cytoplasmic superoxide dismutase activity and lipid peroxidation were found in Wistar rats fed diets containing 1.8 mg/kg/day γ-HCH for 15 or 30 days (Barros et al. 1991). Male Wistar rats fed 13.5 mg lindane/kg/day in their diet for 12 days exhibited decreased activities of liver lipogenic enzymes and increased levels of serum triglycerides (Boll et al. 1995). Focal degeneration of hepatocytes was noted in rabbits given γ-HCH at a dose of 7 mg/kg/day by gavage for 4 weeks (Grabarczyk et al. 1990; Kopec-Szlezak et al. 1989). Rabbits treated with 4.21 mg lindane/kg/day by gavage for 28 days exhibited a significant increase of plasma alkaline phosphatase and alanine aminotransferase activities immediately following initiation of dosing; these activities returned to control levels by day 14 (Cerón et al. 1995). Activity of aspartate aminotransferase also increased immediately following dosing and remained elevated up to 7 days postexposure (day 35). Lindane residues were detected in the blood.

Exposure for 3 months (12 weeks) resulted in increases in liver microsomal mixed-function oxidase activity in rats and mice and a significant increase in absolute and relative liver weights in female rats fed 10.6 and 32.3 mg/kg/day and male and female CF_1 mice fed 21.1 mg/kg/day; histopathological examinations were not performed (Oesch et al. 1982). Liver centrilobular hypertrophy increased in a dose-dependent manner beginning at a dose of 0.4 mg lindane/kg/day in Wistar rats exposed in their diet for 12 weeks (Suter 1983). Liver cell lipospheres were reported in rats fed 2.5 mg γ-HCH/kg/day in the diet for 32 weeks (Ortega et al. 1957). In mice, administration of 90 mg γ-HCH/kg/day in the diet for 24 weeks was reported to result in centrilobular hypertrophy (Ito et al. 1973). Hanada et al. (1973) reported liver cancer in mice fed 78 mg/kg/day in the diet for 32 weeks. Other studies of intermediate-duration exposure (3–48 weeks) have reported slight liver effects or increased liver weight in mice exposed to 18 mg/kg/day of α-HCH, 45 mg/kg/day of β-HCH, and 90 mg/kg/day for δ-HCH and γ-HCH. (Ito et al. 1975). These studies were limited by either a small sample size or lack of statistical analysis.

Chronic exposure of rats to 7–8 mg/kg/day γ-HCH in the diet for 38–70 weeks was reported to result in liver necrosis and fatty degeneration (Fitzhugh et al. 1950). A dose-related increase in periacinal hepatocytic hypertrophy was seen in Wistar rats given 7–8 mg lindane/kg/day in the diet for 104 weeks (Amyes 1990). No liver effects were reported in dogs exposed to 2.9 mg/kg/day for 104 weeks (Rivett et al. 1978). In mice, chronic administration of 13.6–27.2 mg γ-HCH/kg/day in the diet was associated with an increased incidence of liver cancer (NCI 1977; Wolff et al. 1987) (see Section 2.2.2.8).

Similar liver effects were reported in animals following intermediate- or chronic-duration exposure to α-HCH in the diet. Administration of 1.8 mg/kg/day α-HCH in the diet to rats for 15 or 30 days resulted in increases in hepatic cytochrome P-450 content, hepatic lipid peroxidation, and hepatic microsomal superoxide production (Barros et al. 1991). Ito et al. (1975) reported liver cell hypertrophy and hyperplasia in rats exposed to 45 mg/kg/day α-HCH for 24–48 weeks. Hypertrophied liver cells were reported in mice fed 18 mg/kg/day α-HCH and 45 mg/kg/day β-HCH for 24 weeks (Ito et al. 1973), and hepatomegaly was reported in mice exposed to 90 mg/kg/day in the diet for 50 weeks (Tryphonas and Iverson 1983). Liver cancer has also been reported in mice given 18–90 mg α-HCH/kg/day for 16–36 weeks (Hanada et al. 1973; Ito et al. 1973, 1976; Nagasaki et al. 1975; Tsukada et al. 1979) (see Section 2.2.2.8). Long-term exposure to lower doses of α-HCH was reported to result in fatty degeneration and focal necrosis in rats exposed to 3.5–4.0 mg/kg/day for 36–56 weeks (Fitzhugh et al. 1950), and liver cancer was reported in rats administered 50 mg/kg/day in the diet for 72 weeks (Ito et al. 1975).

Significant increases in liver weight and in the levels of hepatic cytochrome P-450, triglycerides, phospholipids, and cholesterol were observed in rats administered 90 mg/kg/day β-HCH in the diet for 2 weeks (Ikegami et al. 1991a, 1991b); decreases in cytochrome c reductase activity were also reported. Intermediate and chronic exposure to β-HCH in the diet is also associated with liver effects in animals. A dose-dependent increase in liver weight was noted in rats exposed for 13 weeks to 0.18–4.5 mg β-HCH/kg/day; the increase was significant at doses of >1 mg/kg/day (Van Velsen et al. 1986). Liver cell hypertrophy was reported in rats fed 25 or 50 mg/kg/day in the diet for 24 or 48 weeks (Ito et al. 1975). In mice, exposure to 45 mg/kg/day for 24 weeks resulted in liver cell hypertrophy (Ito et al. 1973), and exposure to 54–57 mg/kg/day for 32 weeks resulted in hepatic foci of degeneration (Hanada et al. 1973). β-HCH was not found to be carcinogenic in rats or mice exposed for 24–48 weeks (Hanada et al. 1973; Ito et al. 1975). Chronic exposure to lower doses of β-HCH resulted in fatty degeneration and necrosis in the liver of mice fed 3.5–4 mg/kg/day for 36–56 weeks (Fitzhugh et al. 1950), and Thorpe and Walker (1973) reported liver cancer in mice fed 34 mg/kg/day for 26 months.

Liver hypertrophy was observed in rats fed with 45 mg/kg/day of α-, β-, or δ-HCH in the diet for 24 or 48 weeks (Ito et al. 1975) and in mice fed 18 mg/kg/day α-HCH in the diet for 24 weeks (Ito et al. 1973). The toxicity of ingested δ-HCH has not been investigated following chronic exposure.

Technical-grade HCH was reported to cause increases in liver weight and enzymatic activity (e.g., alkaline phosphatase, aminotransferases) in male Swiss mice given 72 mg/kg in the diet for 2 weeks (Ravinder et al.

1989). The same dosing regime also caused significantly increased serum triglycerides, phospholipids, and cholesterol, as well as hypertrophy of hepatocytes with enlargement of nuclei, centrilobular degeneration, and focal necrosis (Ravinder et al. 1990). Statistically significant decreases in the liver activity of glutamic oxaloacetate transaminase (GOT) and lactate dehydrogenase (LD) were observed in pregnant mice administered a single dose of technical-grade HCH (5 mg/kg) on gestation day 9 (Dikshith et al. 1990). Pregnant mice dosed with 25 mg/kg technical-grade HCH experienced a statistically significant decrease in glutamic pyruvic transaminase(GPT) and alkaline phosphatase (AP) activity. Virgin mice administered a single dose of 5–200 mg/kg technical-grade HCH had statistically significant decreases in liver activity of GOT and GPT. Statistically significant increases in liver AP activity were observed in the virgin mice administered 25–200 mg/kg technical-grade HCH. However, with the exception of GOT activity in pregnant mice, the dose response relationships were questionable (Dikshith et al. 1990). There were also no corresponding pathological changes in the liver. Similar effects were seen in male, but not female, rats given 5 or 25 mg/kg/day by gavage for 90 days (Dikshith et al. 1991b). A 65% decrease in liver weight, decreased liver aspartate aminotransferase and lactate dehydrogenase activities, and increased alkaline phosphatase activity were noted in male rats given 60 mg/kg by gavage for 30 days, but animals had normal liver histology (Dikshith et al. 1989a). However, enlargement of hepatocytes, nuclear pyknosis, margination, and vacuolation were observed in rats fed 20 mg/kg/day technical-grade HCH in the diet for 360 days (Dikshith et al. 1991a). No adverse hepatic effects were seen in rats treated with 50 mg/kg/day technical-grade HCH for 30 days (Khanna et al. 1990).

Technical-grade HCH was reported to deplete the hepatic vitamin A content, decrease enzyme activities, and increase liver weight in male rats fed a vitamin A-free diet containing 90 mg/kg/day HCH for 7 weeks (Joseph et al. 1992b). Fatty degeneration and necrosis of the liver were found in rats exposed to 7–8 mg/kg/day of technical-grade HCH for 33–61 weeks (Fitzhugh et al. 1950); these effects were more pronounced at 56–64 mg/kg/day. Mice treated daily with 50 mg/kg/day technical-grade HCH for 1, 5, or 15 days by oil gavage exhibited congestion of hepatic portal vessels and central vein, swollen hepatic cells with vacuolar or parenchymatous degeneration, and fatty changes in periportal and centrilobular cells (Philip et al. 1989). Mice fed diets containing 90 mg/kg/day of HCH for 8 months exhibited increased liver weight, glycogen accumulation, and decreased glucose-6-phosphatase and fructose-1,6-diphosphatase activities (Karnik et al. 1981). Technical-grade HCH was also reported to cause liver cancer in mice following exposure to 90 mg/kg/day in the diet for 2–8 months (Karnik et al. 1981; Thakore et al. 1981) or exposure to 10–50 mg/kg/day for 80–88 weeks (Kashyap et al. 1979; Munir et al. 1983) (see Section 2.2.2.8).

Based on the occurrence of hepatic effects in rats and mice exposed to β-HCH, an intermediate MRL of 0.0006 mg/kg/day has been calculated from the LOAEL of 0.18 mg β-HCH/kg/day (Van Velsen et al. 1986), as described in the footnote in Table 2-3.

An MRL of 0.01 mg/kg/day has been derived for intermediate-duration oral exposure to α-HCH, based on a NOAEL of 1.0 mg/kg/day for hepatic effects in male and female rats (Fitzhugh et al. 1950).

Renal Effects. Progressive renal failure was seen in a woman who died 11 days after intentionally ingesting 8 ounces of a 20% lindane solution (Sunder Ram Rao et al. 1988). The myoglobin release resulting from muscle lysis in this case led to kidney shutdown which was the ultimate cause of death.

Male Fischer-344 rats receiving gavage doses of 10 mg/kg/day of γ-HCH for 4 days showed α-2μ-globulin staining in the kidney cortex. Histopathological changes in the proximal tubule epithelial cells included accumulation of protein droplets, hypertrophy and necrosis, pyknotic nuclei, cellular exfoliation, and regenerative epithelium (Dietrich and Swenberg 1990, 1991). These effects did not occur or were seen to a very slight extent in Fischer-344 male controls, Fischer-344 female exposed rats, or exposed NBR rats (a strain that does not synthesize α-2μ-globulin). These results indicate that damage to male rat kidneys by γ-HCH may be caused by α-2μ-globulin, a protein that is not present in humans. Thus, it is unlikely that humans are at risk for developing this type of pathology from γ-HCH (EPA 1991a). Other biochemical changes indicative of kidney injury, such as significantly increased excretion of glucose in urine, and histological changes, such as hypertrophy and degeneration of the renal tubular epithelia, were observed in Wistar rats exposed to 72 mg/kg/day of γ-HCH for up to 2 weeks (Srinivasan and Radhakrishnamurty 1988; Srinivasan et al. 1984).

However, no renal effects other than significantly increased kidney weight were observed in rats exposed to up to 5–50 mg γ-HCH/kg/day in the diet for up to 40 days (Desi 1974); histological examination of the kidney did not reveal any changes. Slight kidney damage (calcified tubular casts) was reported in rats exposed to 9–10 mg γ-HCH/kg/day for an average of 39.7 weeks (Fitzhugh et al. 1950); the results of this study are limited by poor survival in control and treated animals at all doses. Male rats exposed for 2 years to lindane in their diet exhibited hyaline droplets in the renal proximal tubules at 0.07 mg/kg/day, and pale kidneys, increased kidney weights and urine volumes, and higher urinary protein excretions and tubular necrosis at 7 mg/kg/day (Amyes 1990). Hyaline droplet formation also occurred in a dose-dependent manner in rats treated with 0.02–10 mg lindane/kg/day in their diets for 12 weeks (Suter 1983). Dose-dependent

incidents of renal tubular distension and degeneration were seen in this study beginning at a dose of 2 mg lindane/kg/day.

Fitzhugh et al. (1950) reported kidney damage (nephritis and basal vacuolation) in rats fed 72–80 mg α-HCH/kg/day for an average of 35.9 weeks; no such effects were observed in rats fed 5 mg/kg/day. Poor survival was noted in both control and treated animals.

Renal effects have also been noted in rats exposed to β-HCH in the diet. Srinivasan et al. (1984) reported significantly increased excretion of glucose in urine and increased excretion of creatinine and urea as well as hypertrophy and degeneration of the renal tubular epithelia in rats exposed to 72 mg β-HCH/kg/day for up to 2 weeks. Van Velsen et al. (1986) reported significantly increased kidney weights in female rats exposed to 0.18 mg β-HCH/kg/day for 13 weeks; males did not show a significant increase until they were exposed to a dose of 4.5 mg/kg/day. At 22.5 mg/kg/day, both males and females exhibited renal calcinosis in the outer medulla; however, the female controls also exhibited calcinosis. The study authors noted that renal calcinosis is common in female rats but that this finding was of significance in males (Van Velsen et al. 1986). Fitzhugh et al. (1950) also examined the renal effects of exposure to β-HCH in rats that died after an average of 4.4 weeks and found nephritis and basal vacuolation similar to that described in rats exposed to α-HCH; poor survival due to unspecified causes was reported in both control and treated animals.

Nephritis, pigmentation, and basal vacuolation were also observed in rats fed 56–64 mg technical-grade HCH/kg/day (64% α-HCH, 10% β-HCH, 13% γ-HCH, 9% δ-HCH, and 1.3% ε-HCH) in the diet for an average of 32.9–64.6 weeks (Fitzhugh et al. 1950); poor survival (for which there was no explanation) was noted in both control and treated animals. Tubular necrosis and glomerular degeneration was seen in animals exposed for 360 days to 20 mg/kg/day of technical-grade HCH (Dikshith et al. 1991a), but no renal effects were seen in rats exposed to 60 mg/kg/day technical-grade HCH for 30 days by oil gavage (Dikshith et al. 1989a). Mice treated daily with 50 mg/kg/day technical-grade HCH for 1, 5, or 15 days by oil gavage exhibited congestion of blood vessels and glomerular tufts, swollen tubules with hyaline casts, cystic dilation, fatty changes, some interstitial hemorrhaging in the medulla, and epithelial cell vacuolation (Philip et al. 1989). No adverse effects were seen in rats treated with 50 mg/kg/day technical-grade HCH for 30 days (Khanna et al. 1990).

Endocrine Effects. No studies were located regarding endocrine effects in humans or animals following oral exposure to HCH.

Body Weight Effects. No studies were located regarding body weight effects in humans following oral exposure to HCH.

Significantly decreased body weight gain has been seen in rats treated orally with 800 ppm α- (Fitzhugh et al. 1950), 250 mg/kg feed β- (Fitzhugh et al. 1950; Van Velsen et al. 1986), 40 mg/kg/day γ- (Fitzhugh et al. 1950; Laws et al. 1994), and 10 or 20 mg/kg/day technical-grade HCH (Gautam et al. 1989; Joseph et al. 1992b; Nagaraja and Desiraju 1994).

Metabolic Effects. No studies were located regarding metabolic effects in humans following oral exposure to HCH.

Increased phosphoinositide turnover and generation of second messengers from phosphoinositides were seen in erythrocyte membranes from female rats treated by gavage with a single dose of 100 mg/kg technical-grade HCH, or with doses of 5 mg/kg/day technical-grade HCH for 3–6 months, 5 days/week (Agrawal et al. 1995). The latter exposure regime also resulted in a significant decrease in phosphatidylinositol, phosphatidylinositol 4-phosphate, and phosphatidylinositol 4,5-bisphosphate in erythrocyte membrane and cerebrum; the levels decreased with increased time of treatment (3–6 months).

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans following oral exposure to HCH.

Some evidence of possible immunotoxic effects of γ-HCH is available from animal studies. Immuno-suppression, as measured by decreased agglutinin titers against typhoid vaccine and *Salmonella* vaccine, was reported in rats exposed by gavage to 6.25 and 25 mg γ-HCH/kg/day for 5 weeks (Dewan et al. 1980) and in rabbits exposed by capsules 5 times each week to 1.5, 6, and 12 mg/kg/day for 5–6 weeks (Desi et al. 1978). Dose related decreases in thymus and spleen weights were observed in mice gavaged with 10–20 mg/kg/day γ-HCH for 10 days and decreased thymus weight was observed in mice gavaged with 20–40 mg/kg/day γ-HCH for 3 days (Hong and Boorman 1993). The primary antibody response to sheep red blood cells was

suppressed in albino mice after exposure to 9 mg/kg/day γ-HCH in their diet for 12 weeks (Banerjee et al. 1996). Suppression of secondary antibody response was also observed after 3 weeks exposure to 9 mg/kg/day γ-HCH and after 12 weeks of 5.4 mg/kg/day lindane exposure. Decreased lymphoproliferative responses to mitogens were seen in mice exposed to 60 mg/kg/day β-HCH in the diet for 30 days (Cornacoff et al. 1988). There were no associated changes in immunoglobulins, red blood cell counts, or histology of the thymus, spleen, or lymph nodes. Cortical atrophy of the thymus was observed in rats fed 22.5–25 mg/kg/day β-HCH (Van Velsen et al. 1986). A biphasic dose-dependent immunological effect of γ-HCH on components of cell- and humoral-mediated immunity, characterized by initial stimulation followed by immunosuppression, was reported in mice fed 0.012, 0.12, or 1.2 mg γ-HCH/kg/day for 24 weeks (Meera et al. 1992). In addition, histological examinations revealed decreased lymphocyte populations in the thymus and lymph nodes and a reduction in overall cellularity in the spleen and necrosis of the thymus at 1.2 mg/kg/day. The LOAEL values for immunological effects are recorded in Tables 2-2 and 2-3 and plotted in Figures 2-2 and 2-3.

Based on immunological effects of γ-HCH on components of cell- and humoral-mediated immunity in mice, an intermediate MRL of 1×10^{-5} mg/kg/day has been calculated from the LOAEL of 0.012 mg γ-HCH/kg/day (Meera et al. 1992), as described in the footnote in Table 2-2.

2.2.2.4 Neurological Effects

In humans, the most commonly reported effects associated with oral exposure to γ-HCH are neurological. Most of the information is from case reports of acute γ-HCH poisoning. No studies were located regarding neurological effects in humans following long-term ingestion of α-, β-, γ-, or δ-HCH. Seizures and convulsions have been observed in individuals who have accidentally or intentionally ingested γ-HCH in insecticide pellets, liquid scabicide, or contaminated food (Davies et al. 1983; Harris et al. 1969; Munk and Nantel 1977; Powell 1980; Starr and Clifford 1972; Storen 1955). In most cases, exposure to γ-HCH was inferred from the presence of γ-HCH in the urine or blood. Also, the actual amount of γ-HCH ingested could not be determined because the γ-HCH was present in solution or in pellets in which other substances were present. Liquid scabicide has been reported to contain approximately 1% γ-HCH (Davies et al. 1983; Powell 1980).

Neurotoxic effects have been reported in several species of animals exposed to γ-HCH. The most serious effects were seizures following a single intragastric administration of approximately 15–60 mg/kg in rats

(Martinez and Martinez-Conde 1995; Martinez et al. 1991; Tilson et al. 1987; Tusell et al. 1987; Vendrell et al. 1992a, 1992b; Woolley and Griffith 1989). Treatment of rats with a single dose of 30 mg lindane/kg by gavage resulted in convulsions 10–30 minutes later, with molecular analysis revealing the repression of calmodulin (CAM) genes, in particular, decreased levels of mRNA from the CAM II gene (Barrón et al. 1995a). Less-serious effects in rats included increased anxiety following a single gavage dose of 20 mg/kg (Llorens et al. 1990b) and increased spontaneous motor behavior observed at 10 mg/kg (Llorens et al. 1989).

Kindling, the induction of seizures with repeated application of subthreshold electrical or chemical stimuli, has been used as a method of investigating neurological response to HCH poisoning. A single oral dose of 5–20 mg lindane/kg to rats previously kindled by electrical stimulus produced incidences of myoclonic jerks and clonic seizures which increased in a dose-dependent manner (Gilbert and Mack 1995). Nonkindled animals displayed these symptoms at a dose of 10 mg lindane/kg. Enhanced susceptibility to kindled seizures brought on by electrical stimulation was seen in rats exposed for 10 weeks to 10 mg lindane/kg/day, 3 days/week (Gilbert 1995). Increased rates of acquisition of kindled seizures were observed following dosing of rats with 3–10 mg lindane/kg/day for 4 days (Joy et al. 1982). An MRL of 0.01 mg/kg/day has been derived for acute-duration oral exposure to γ-HCH, based on a NOAEL of 1 mg/kg/day for increased kindling acquisition (Joy et al. 1982).

Eleptiform seizures have been reported in male rats fed milk, from dams that were gavaged with 20 mg γ-HCH/kg, on postnatal days 3–15 (Albertson et al. 1985). These data suggest that γ-HCH can be transferred in the dam's milk and elicit neurological effects in offspring. It is not possible to determine the doses received by the pups. Avoidance response latency was statistically increased in rats administered a single dose of 15 mg/kg by gavage (Tilson et al. 1987). No clinical signs of behavioral effects were seen in suckling Wistar rats treated once with 20 mg/kg lindane by gavage at postnatal days 8, 15, 22, or 29, although regional changes in brain noradrenaline and serotonin were seen, with differential effects depending on age at the time of exposure (Rivera et al. 1991).

Changes in levels of brain norepinephrine (Rivera et al. 1991) and serotonin (Attia et al. 1991; Rivera et al. 1991) have also been reported in rats administered acute oral doses of γ-HCH. Decreased dopamine levels were seen in rats treated by gavage with 10 doses totaling 60 mg lindane/kg (half the LC_{50}) over a period of 30 days (Martinez and Martinez-Conde 1995). Increase in the levels of brain catecholamines, particularly norepinephrine and dopamine, and associated signs of toxicity such as mild tremor, lacrimation, salivation, and dysnea were observed in female rats given oral doses of 100 mg/kg/day of technical-grade HCH for

7 days (Raizada et al. 1993). The activity of monoamine oxidase (MAO) in the cerebrum showed a marginal decrease; while the cerebellum and spinal cord indicated a significant increase and decrease in MAO, respectively. Rats treated with 20 mg technical-grade HCH/kg/day in food for 90 days exhibited increased γ-aminobutyric acid (GABA) levels, increased glutamate decarboxylase (GAD) activity, and decreased glutamate levels in the brain (Nagaraja and Desiraju 1994). No significant changes were seen in lipid peroxidation in brain tissue from rats treated for 90 days with 90 mg lindane/kg/day in food, indicating that the tonic convulsions observed throughout the exposure period were probably not brought on by oxidative stress in the brain (Arisi et al. 1994). Decreased myelin basic protein was observed in rats exposed to 5 mg/kg/day by gavage for 3 days (Serrano et al. 1990a).

Longer exposures to lower doses of γ-HCH were reported to result in significantly altered Skinner box behavior (operant conditioning) in a small number of rats exposed to 2.5 mg/kg/day for 40 days (Desi 1974), and significantly decreased nerve conduction velocity in rats exposed to 25.4 mg/kg/day for 30 days (Muller et al. 1981). The latter study did not examine any behavioral parameters.

Similar neurological effects have not been reported in animals treated with α-HCH. Muller et al. (1981) reported no delay in tail nerve conduction velocity in rats fed 5.1, 54.2, or 106.2 mg α-HCH/kg/day for 30 days. However, neurological effects have been reported in rats exposed to β-HCH. Mice treated with 57 or 190 mg/kg/day β-HCH for 30 days developed ataxia within 1 week of treatment (Cornacoff et al 1988). An acute-oral MRL of 0.2 mg/kg/day was derived based on a NOAEL of 19 mg/kg/day for ataxia. The study was limited by small sample size (6 per group) and lack of quantificative and dose-response information. Muller et al. (1981) reported a significant delay in tail nerve conduction velocity in rats fed 66.3 mg β-HCH/kg/day for 30 days. Van Velsen et al. (1986) reported ataxia and coma in rats exposed to 22.5–25 mg β-HCH/kg/day for 13 weeks. Rats treated once with 100 mg δ-HCH/kg by gavage exhibited no convulsions, although molecular analysis revealed a significant decrease in mRNA expression from brain calmodulin (CAM) genes (Barrón et al. 1995). Seizures were noted in mice exposed to technical-grade HCH through feed or gavage at levels of 10–17 mg/kg/day in the feed for 80 weeks (Kashyap et al. 1979). A significant increase in motor activity was noted in rats exposed to technical-grade HCH at a level of 50 mg/kg/day for 120 days (Gopal et al. 1992); a significant decrease in rearing (sitting back on haunches) was seen in rats exposed to 50 mg/kg/day technical-grade HCH and fed a protein-deficient diet. Alterations in neurotransmitter levels, increased brain wave frequency, and behavioral changes were reported in male rats administered 50 mg/kg/day technical-grade HCH by gavage for 1 or 3 months (Anand et al. 1991). Exposure to 0.4 mg/kg/day technical-grade HCH for 360 days resulted in convulsions, tremors, and paralysis in male

rats after 270 days, although the number of animals affected or the severity of the symptoms were not reported (Dikshith et al. 1991a). This study also found degeneration of the cerebellum and cerebellar cortex in animals sacrificed after a one-year exposure to 20 mg/kg/day.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to HCH.

Increased length of estrous cycle and decreased sexual receptivity were found in female rats treated with a single dose of γ-HCH (25 mg/kg) given by gavage (Uphouse and Williams 1989). Inhibition of the formation of estradiol-receptor complex in the rat uterus cytosol was reported in female rats administered 30 mg γ-HCH/kg/day by oral intubation for 7 days (Tezak et al. 1992). Female mink treated with 1 mg/kg/day γ-HCH in their diet from 6 weeks before mating until weaning showed a decrease in receptivity to a second mating and a decrease in whelping rate, although litter size was not affected (Beard et al. 1997). This decreased fertility effect was primarily a result of embryo mortality after implantation. Mouse dams treated with γ-HCH (6.2 mg/kg) during gestation period days 6–12 had increased numbers of resorbed fetuses (Sircar and Lahiri 1989). A lack of implantation sites and pups death were observed following treatment with 10.8 mg/kg/day on gestation days 1–4 and 3.6 mg/kg/day on gestation days 14–19, respectively. Statistically significant increases in the glycogen content of the uterus, cervix, and vagina (but no increase in organ weight) were reported in female rats exposed to 20 mg γ-HCH/kg/day in the diet for 30 days (Raizada et al. 1980). Antiestrogenic properties were found in female rats given oral gavage doses of 10 mg/kg/day γ-HCH for 15 weeks (Chadwick et al. 1988). These responses were not seen at 5 mg/kg/day. Ovariectomized rats exposed for 5 days and sexually immature female rats exposed for 7 days to 40 mg lindane/kg/day showed no effects on the number of estrogen and estrogen-dependent progesterone receptors (Laws et al. 1994). Thus, lindane's antiestrogenic effects in reproductive tissue do not appear to be due to direct action on estrogen receptors or its induction of progesterone receptors. Female rabbits exposed to 0.8 mg γ-HCH/kg/day, 3 days/week for 12 weeks, had a reduced ovulation rate (Lindenau et al. 1994). However, rabbits given the same treatment regime followed by artificial insemination exhibited no effects on the fertilization rate or on pre- or postimplantation losses (Seiler et al. 1994). In male rats, oral administration of 6 mg/kg for 5 days or a single dose of 30 mg/kg of γ-HCH resulted in a reduction in the number of testicular spermatids and epididymal sperms of both treated groups 2 weeks after treatment (Dalsenter et al. 1996). γ-HCH was detected in the testes of both groups 24 hours and 2 weeks after the last treatment. Histological examination by electron microscopy revealed ballooning of the Sertoli cells with

fragmentation or loss of organelles. Similarly, Shivanandappa and Krishnakumari (1983) reported testicular atrophy, degeneration of seminiferous tubules, and disruption of spermatogenesis in male rats fed 75 mg γ-HCH/kg/day for 90 days. Significant reductions in the relative weight of testicles and epididymis, spermatid and sperm counts, and testosterone levels were observed in pubescent or adult rats fed milk as neonates from dams gavaged with 6 mg/kg γ-HCH on lactation day 9 or 14 or 1 mg/kg γ-HCH on lactation days 9–14 (Dalsenter 1997). Histopathological observations included a reduction in Leydig cell numbers and spermatogenesis. However, fertility, measured by impregnation of female rats, was unaffected. Rats exposed to approximately 10 mg/kg/day for 4 generations showed no adverse reproductive effects (Palmer et al. 1978b).

Oral exposure to 60 mg β-HCH/kg for 30 days resulted in normal uteri and reproductive cycling in female mice (Cornacoff et al. 1988). Atrophy of the ovaries and testes, hyperplastic and vacuolized endometrial epithelium, degeneration of the seminiferous tubules, and disruption of spermatogenesis were seen in rats exposed to 22.5–25 mg β-HCH/kg/day in their diet for 13 weeks (Van Velsen et al. 1986). Technical-grade HCH caused transient changes in testes' weights and decreased sperm counts in a 7-week study (Pius et al. 1990), degeneration of seminiferous tubules and Leydig cells (Roy Chowdhury and Gautam 1990), and changes in the muscle layer of the seminiferous tubules (Gautam et al. 1989). None of these studies provide adequate evidence for the effects of technical-grade HCH on sperm function in animals or humans.

In mice, exposure to 90 mg technical-grade HCH/kg/day (isomer composition unknown) for 3 months led to increased testicular weight and degeneration of seminiferous tubules (Nigam et al. 1979). Testicular degeneration was reported in male rats exposed to 20 mg/kg/day technical-grade HCH in the diet for 360 days (Dikshith et al. 1991a). A dose-related increase in fetal resorptions was seen in pregnant female mice treated once with 25–200 mg/kg technical-grade HCH by gavage on the ninth gestation day (Dikshith et al. 1990).

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to any of the HCH isomers.

A single oral dose of 25 mg/kg technical-grade HCH caused increased resorptions of the fetus in female mice, but fetal development was normal (Dikshith et al. 1990). Srivastava and Raizada (1993) further studied the

prenatal effect of orally administered technical-grade HCH. While mice exposed to HCH during the preimplantation period (day 2–6 of gestation) did not show fetolethality, exposure during the postimplantation period (day 6–12 of gestation) to 25 and 50 mg/kg/day HCH produced significant increases in resorption of fetuses, inhibition of maternal serum progesterone levels, and higher levels of HCH in fetal tissues. Oral exposure to Benesan (a pesticidal formulation containing 50% γ-HCH) given at doses of 6.25, 12.5, or 25 mg/kg/day by gavage on days 6–15 of gestation failed to produce teratogenic effects in rats (Khera et al. 1979). When minks were treated with 1 mg/kg/day γ-HCH in their diet (Beard et al. 1997), the proportion of embryos lost after implantation was increased. In another study, γ-HCH was administered to pregnant mice by gastric intubation on day 12 of gestation. At doses of 30 and 45 mg/kg body weight in C57BL/6J mice, significant decreases in fetal weight, fetal thymic weight, and placental weight were observed (Hassoun and Stohs 1996a). When given to DBA/2J mice at a dose of 45 mg/kg body weight, γ-HCH caused significant reduction in fetal and placental weight. No malformations in the fetuses of both strains of mice were observed, even though the administered doses caused maternal deaths. Increases in the production of lipid metabolites in maternal sera and the amniotic fluids were found to parallel the observed fetotoxicities (Hassoun et al. 1996). Superoxide production, lipid peroxidation and DNA-single strand breaks were increased in fetal and placental tissues 48 hours after administration of single dose of 30 mg/kg γ-HCH to pregnant mice on day 12 of gestation (Hassoun and Stohs 1996b). Significant increases in lipid peroxidation also occurred in fetal livers collected on day 18 of gestation. Thus, it was suggested that fetotoxic effects of γ-HCH may be due to induced oxidative stress, enhanced lipid peroxidation, and DNA-single strand breaks in the fetal and placental tissues of mice. In another study, γ-HCH given to rat dams during gestation and lactation did not cause developmental effects in the pups, but β-HCH (20 mg/kg/day during gestation) caused increased fetal deaths within 5 days of birth and exposure to 5 mg/kg/day during gestation and lactation resulted in increased liver weights of pups (Srinivasan et al. 1991a). When lactating female rats were treated orally with a single dose of 6 mg/kg of γ-HCH on day 9 or 14, or 1 mg/kg on days 9–14 of lactation; the testosterone level of the male offspring was reduced 50% at puberty (day 60) when compared to the control group (Dalsenter et al. 1997a). When the offspring reached adulthood (day 140 postnatal), the relative testicular weight was significantly lower (Dalsenter et al. 1997). The number of sperm and spermatids was also significantly reduced. A dose-related increase in the incidence of fetuses with an extra 14th rib was reported in CFY rats exposed to 5, 10, or 20 mg/kg γ-HCH by gavage during gestation days 6–15; statistical significance was attained only at 20 mg/kg (Palmer et al. 1978a). The incidence of fetuses with an extra 13th rib was statistically increased in rabbits exposed to 20 mg/kg γ-HCH by gavage during gestation days 6–18 (Palmer et al. 1978a). In both rats and rabbits, the incidences of extra ribs were within or just greater than the ranges recorded for the control groups, and therefore, may not be sufficient

evidence of teratogenicity caused by exposure to γ-HCH. No effects on embryonic development were seen in rabbits treated by oral gavage with 0.8 mg lindane/kg, 3 times per week for 12–15 weeks before artificial insemination and throughout gestation (Seiler et al. 1994). Regional changes in brain noradrenaline, serotonin and the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) levels were noted in suckling rats treated with 20 mg/kg/day γ-HCH, as a single dose (Rivera et al. 1991). Alterations in levels of brain dopamine, serotonin, gamma-aminobutyric acid ($GABA_B$), glutamate, glutamate decarboxylase, and noradrenaline were seen in various areas of the brains of female rat pups treated with 10 mg technical-grade HCH/kg/day for 60 days (Nagaraja and Desiraju 1994).

2.2.2.7 Genotoxic Effects

No studies were located regarding genetic effects in humans following oral exposure to HCH.

In animals, ingestion of technical-grade HCH was reported to induce dominant lethal mutations in mice (Lakkad et al. 1982). Oral exposure to α-HCH was reported to result in mitotic disturbances including an increased mitotic rate and an increased frequency of polyploid hepatic cells in rats (Hitachi et al. 1975). Incidence of chromosome clastogeny in bone marrow cells was increased in mice exposed for 7 days to 1.6 mg γ-HCH/kg/day (Kumar et al. 1995).

Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding the carcinogenicity of the individual isomers of HCH or technical-grade HCH following ingestion by humans.

α-HCH, β-HCH, γ-HCH, and technical-grade HCH have been shown to be liver carcinogens in rats and mice; however, in some studies the liver was the only organ examined. Ito et al. (1973) examined the carcinogenicity of HCH isomers in dd mice exposed to 45 mg/kg/day of each isomer (total dosage was 90 mg/kg/day) for 24 weeks. Exposure to β-, γ-, or δ-HCH alone did not result in hepatocellular carcinoma. However, when these isomers were mixed with α-HCH, hepatocellular carcinoma was observed. These results suggest that α-HCH is itself a hepatocellular carcinogen or acts synergistically with the other isomers.

In Wistar rats, exposure to 25 mg γ-HCH/kg/day in the diet for 24 or 48 weeks did not result in any identifiable carcinogenic effect (Ito et al. 1975); however, high mortality in the control and treatment groups precludes determination that γ-HCH is not carcinogenic to rats under this experimental protocol. Mice (dd strain) exposed to as much as 90 mg γ-HCH/kg/day in the diet for 24 weeks did not exhibit any carcinogenic effects (Ito et al. 1973). Although an increased incidence of malignant hepatomas was reported in male dd mice exposed to 108–120 mg/kg/day in the diet for 32 weeks (Hanada et al. 1973), this dose level may have exceeded the maximum tolerated dose (MTD), based on effects of γ-HCH on survival. Liver nodules developed in mice receiving 39 mg/kg/day of γ-HCH, although the number of animals tested was small, the study was limited by the lack of statistical analysis.

Information concerning the cancer effects of γ-HCH following chronic-feeding exposure is equivocal. No statistically significant increases in endocrine, thyroid, pituitary, adrenal gland, liver, or ovary tumors were observed in male and female Osborne-Mendel rats fed 10.8–33 mg/kg/day in the diet for 80 weeks (NCI 1977) and in Wistar rats fed 0.07–32 mg γ-HCH/kg/day in the diet for 104 weeks (Amyes 1990); however, poor survival rates limit the significance of these results. On the other hand, hepatocellular carcinomas have been reported in CF_1 and $B6C3F_1$ mice exposed to 13.6–27.2 mg/kg/day in the diet for 80 or 104 weeks, respectively (NCI 1977; Wolff et al. 1987). In addition, hepatocellular carcinomas have been reported in yellow (YS/UY)F-1 mice exposed to 27.2 mg/kg/day in the diet for 96 weeks (Wolff et al. 1987); this strain of mouse has a dominant mutation at the agouti locus (A^{vy}) that results in an increased susceptibility to formation of strain-specific neoplasms. The human oral carcinogenicity assessment for γ-HCH is currently under review (IRIS 1998).

No evidence of liver carcinogenicity was reported in Wistar rats exposed to 45 or 90 mg α-HCH/kg/day in the diet for 24 or 48 weeks (Ito et al. 1975; Nagasaki et al. 1975); high mortality was observed in both the treated and control groups. However, α-HCH appears to be carcinogenic in mice following intermediate-duration exposure. Hepatomas and hepatocellular carcinomas have been reported in a number of strains of mice exposed to 13–95 mg/kg/day for 16–36 weeks (Hanada et al. 1973; Ito et al. 1973, 1976; Nagasaki et al. 1975; Tsukada et al. 1979). Tryphonas and Iverson (1983), however, reported no evidence of a carcinogenic effect in male mice exposed to 90 mg α-HCH/kg/day in the diet for 50 weeks. Ito et al. (1975) reported an increased incidence of hepatocellular carcinoma in male rats exposed to 50 and 75 mg α-HCH/kg/day in the diet for 72 weeks, suggesting that α-HCH may be carcinogenic in rats after long-term exposure. A study of enzyme-altered liver foci in rats treated first with the tumor initiator *N*-nitrosomorpholine, and then 20 mg α-HCH/kg/day in food for 49 weeks, found that the tumor promoter activity of HCH is apparently due to

increased cell proliferation caused by a lowering of the cell death (apoptosis) rate (Luebeck et al. 1995). In another study in rats, additional administration of 35 mg/kg/day of α-HCH in the diet for 65 weeks inhibited the induction of liver tumors by 0.07 mg/kg/day of aflatoxin B_1 (Angsubhakorn et al. 1981). IRIS (1998) lists α-HCH as a probable human carcinogen and estimated an oral cancer potency factor for α-HCH of 6.3 $(mg/kg/day)^{-1}$ based on the incidence of hepatic nodules and hepatocellular carcinomas observed in male mice administered α-HCH in the diet (Ito et al. 1973). The oral cancer potency factor is a plausible upper-bound estimate of the lifetime probability of an individual developing cancer as a result of oral exposure per unit intake of the chemical.

β-HCH has not been found to be carcinogenic in Wistar rats exposed to 25 or 50 mg/kg/day in the diet for 24 or 48 weeks (Ito et al. 1975) or in dd mice exposed to 18–120 mg/kg/day in the diet for 24 or 32 weeks (Hanada et al. 1973; Ito et al. 1973). However, Thorpe and Walker (1973) reported an increased incidence of hepatocellular carcinomas in CF1 mice exposed to 26 mg/kg/day in the diet for 104 weeks. The studies with negative results were, in general, of short duration, used a small number of animals, or failed to examine all of the animals. IRIS (1998) lists β-HCH as a possible human carcinogen and estimated an oral cancer potency factor for ingested β-HCH of 1.8 $(mg/kg/day)^{-1}$ based on the incidence of hepatic nodules and hepatocellular carcinomas observed in male mice administered β-HCH at a single dose level in the diet (Thorpe and Walker 1973). This is the only chronic study from which to estimate cancer risk from exposure to β-HCH. The study is limited by the use of only one nonzero dose group. Also, the use of incidence of liver tumors alone in mice to predict a compound's carcinogenicity in humans may be equivocal (Vesselinovitch and Negri 1988). Diversity of factors has been shown to influence the development of liver cell tumors in mice, such as the strain of the mice (Nagasaki et al. 1975b), the protein or calorific value of the diet (Tannenbaum and Silverstone 1949), and the microbial flora of the animals (Roe and Grant 1970).

δ-HCH has not been found to be carcinogenic in male Wistar rats exposed to 45 or 90 mg/kg/day in the diet for 24 or 48 weeks (Ito et al. 1975) or in male dd mice exposed to 18–90 mg/kg/day in the diet for 24 weeks (Ito et al. 1973). However, these studies were of relatively short-exposure duration. δ-HCH is structurally related to carcinogenic HCH isomers, but it is currently listed as not classifiable for human carcinogenicity (IRIS 1998).

Increased incidence of carcinoma was reported in Swiss mice following exposure to 90 mg technical-grade HCH/kg/day in the diet for 8–32 weeks (Thakore et al. 1981). Increased incidences of hepatocellular carcinoma were also reported in Swiss mice exposed to 21.3–85 mg/kg/day in the diet for 20 months (Munir

et al. 1983) and in Swiss mice exposed to 10 or 17 mg/kg/day through gavage or the diet, respectively, for 80 weeks (Kashyap et al. 1979).

2.2.3 Dermal Exposure

Studies examining the dermal toxicity of HCH in humans are limited. Most of the available information is obtained from cases in which γ-HCH was dermally applied as a scabicide. γ-HCH in topical creams and lotions is efficiently absorbed through the skin (Ginsburg et al. 1977). Although it has been reported that these lotions contain 1% γ-HCH, it is not possible to quantify the amount of γ-HCH to which these individuals were exposed, because of the different areas of skin treated.

2.2.3.1 Death

No studies were located regarding lethal effects in humans following dermal exposure to α-, β-, or δ-HCH. An acute whole-body dermal application of 1% γ-HCH lotion to a 2-month-old infant for the treatment of scabies was reported to result in death (Davies et al. 1983), and a concentration of 110 ppb γ-HCH was identified in the brain. In general, most humans dermally poisoned with γ-HCH have recovered with no apparent adverse effects (Fagan 1981).

In animals, acute dermal exposure to high doses of γ-HCH were reported to result in death. The dermal LD_{50} for γ-HCH is 900 mg/kg in female rats and 1,000 mg/kg in male rats (Gaines 1960). Rats exposed to moistened lindane for 24 hours exhibited no mortality at 250 mg/kg, 20% mortality at 600 mg/kg, 40% mortality at 1,000 mg/kg, and 30% mortality at 2,000 mg/kg (Ullmann 1986a). Significant lethality (47%) was seen in female rats, but not male rats, exposed dermally to 400 mg γ-HCH/kg/day for 13 weeks, 5 days/week, 6 hours/day (Brown 1988). Calves dermally exposed to 33.3 mg/kg γ-HCH died within 5 months (Venant et al. 1991). Dikshith et al. (1978) reported that guinea pigs dermally exposed to 200 mg technical-grade HCH/kg died within 5–12 days. Four of 20 rats died from exposure to technical-grade HCH at 100 mg/kg/day for 15–30 days (Dikshith et al. 1991c). Weanling rabbits were more sensitive to γ-HCH treatment than young adults, as seen by increased mortality rates accompanied by excitement and convulsions after a single whole-body treatment with a 1% solution at a dose of 60 mg γ-HCH/kg (Hanig et al. 1976). This suggests that children might be at a greater risk than adults for toxic responses to dermal absorption of HCH. Rabbits treated with 25 mg/kg/day technical-grade HCH for 30 days by skin painting on shaved dorsal, ventral, or thigh areas exhibited no deaths in the group exposed by dorsal application, but 2 of

8 rabbits died in the group exposed by ventral application, and 4 of 8 died in the group exposed by thigh application (Dikshith et al. 1989b). These and other values are in Tables 2-4 and 2-5.

2.2.3.2 Systemic Effects

Reliable LOAELs for respiratory, hepatic, and renal effects in animals after acute and intermediate exposure to γ-HCH are shown in Table 2-4. Reliable LOAELs for hepatic, renal, and dermal effects in animals after intermediate exposure to technical-grade HCH are shown in Table 2-5.

Respiratory Effects. An acute dermal poisoning of a 2-month-old infant exposed to a whole body application of 1% γ-HCH lotion resulted in death. The autopsy revealed pulmonary petechiae (tiny reddish spots that contain blood) (Davies et al. 1983). Slight dyspnea was observed in rats exposed dermally for 24 hours to 1,000 or 2,000 mg γ-HCH/kg on a shaved patch of dorsal skin (Ullmann 1986a). The dyspnea was severe in one female administered the high dose. Rapid respiration or wheezing was noted in rats exposed dermally to 10 mg γ-HCH/kg/day for 13 weeks (Brown 1988).

Cardiovascular Effects. An acute dermal poisoning of a 2-month-old infant exposed to a whole-body application of 1% γ-HCH lotion resulted in death. The autopsy findings were minimal but revealed epicardial petechiae (Davies et al. 1983).

No studies were located regarding cardiovascular effects in animals following dermal exposure to HCH.

Gastrointestinal Effects. Vomiting and diarrhea occurred in a child who had 1% γ-HCH applied to the skin to treat a rash (Ramchander et al. 1991).

No studies were located regarding gastrointestinal effects in animals following dermal exposure to HCH.

Hematological Effects. Aplastic anemia was documented in a man who applied γ-HCH to his skin for 3 weeks for treatment of scabies (Rauch et al. 1990). Excessive dermal exposure to HCH was reported to result in aplastic anemia and bone marrow hyperplasia in a woman who bathed her dog once a week for 2 years in a preparation that reportedly contained 2% HCH (Woodliff et al. 1966). Reduced hemoglobin and hematocrit values and a nearly complete absence of red blood cell precursors in bone marrow were reported in

TABLE 2-4. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Dermal

Species (strain)	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
ACUTE EXPOSURE						
Death						
Rat (Sherman)	10 d once				1,000 M (LD_{50})	Gaines 1960
					900 F (LD_{50})	
Rat (Wistar)	24 hr once				1,000 (LD_{50})	Ullmann 1986a
Systemic						
Rat (Wistar)	24 hr once	Resp	600	1,000 (dyspnea)		Ullmann 1986a
Rabbit (New Zealand)	once	Ocular		40 (mild eye irratation)		Ullmann 1986c
Rabbit (New Zealand)	4 hr once	Dermal	200			Ullmann 1986d
Neurological						
Rat (Wistar)	24 hr once		600	1,000 (slight sedation)	2,000 F (severe spasms)	Ullmann 1986a
INTERMEDIATE EXPOSURE						
Death						
Rat (Crl:(WI)BR)	13 wk 5 d/wk 6 hr/d		60 F		400 F (23 deaths out of 49)	Brown 1988

TABLE 2-4. Levels of Significant Exposure to Gamma-Hexachlorocyclohexane (Lindane) - Dermal (continued)

Species (strain)	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
Systemic						
Rat (Crl:(WI)BR)	13 wk 5 d/wk 6 hr/d	Resp		10 (rapid respiration or wheezing)		Brown 1988
		Hepatic	10	60 (centrilobular hypertrophy)		
		Renal		10 M (hyaline droplet formation		
		Renal	10 F	60 F (basophilic tubules)		
Rat	once for 25 days			180 F (mild dermatitis)		Dikshith et al. 1973
Neurological						
Rat (Crl:(WI)BR)	13 wk 5 d/wk 6 hr/d			10 (hyperactivity)	60 F (ataxia, tremors, convulsions)	Brown 1988

d = day(s); F = female; hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s).

TABLE 2-5. Levels of Significant Exposure to Technical - Grade Hexachlorocyclohexane - Dermal

Species (strain)	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL		Reference/ Chemical Form
				Less serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE						
Death						
Gn pig (NS)	5-12 d 1x/d				200 M (24/24 deaths)	Dikshith et al. 1978 technical
INTERMEDIATE EXPOSURE						
Death						
Rat (Wistar)	15 d 1x/d				100 F (2/10 deaths)	Dikshith et al. 1991c technical
Rabbit (NS)	30 d 1x/d				25 M (6/24 deaths)	Dikshith et al. 1989b technical
Systemic						
Rat (Wistar)	30 d 1x/d	Hepatic			100 F (hypertrophy, fatty degeneration, nuclear pyknosis of hepatocytes, diffuse and focal liver necrosis)	Dikshith et al. 1991c technical
		Renal			100 F (tubular necrosis)	
		Dermal		100F (hyperkeratosis, epidermal cell vacuolization, thickening of collagen fibers)		

TABLE 2-5. Levels of Significant Exposure to Technical - Grade Hexachlorocyclohexane - Dermal (continued)

Species (strain)	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ Chemical Form
Rabbit (NS)	30 d 1x/d	Hepatic		25M (hepatocyte degeneration, pycnotic nuclei, enlarged liver, altered GOT, GPT, LDH, and ALP activities)		Dikshith et al. 1989b technical
		Renal			25 M (altered epithelial lining of proximal convoluted tubules, loss of brush borders of tubules, atrophy of glomerular capsules)	
		Dermal		25M (thickened epidermis, hyperkeratinization, and infiltration of mononuclear cells)		
Gn pig (NS)	30 d 1x/d	Hepatic		100M (38% increase in liver weight, hepatic hypertrophy, pycnotic nuclei in cytoplasm, focal fatty inclusions, increased GOT and ALP activity)		Dikshith et al. 1978 technical
		Renal	100 M			
CHRONIC EXPOSURE						
Cancer						
Mouse (Swiss)	80 wk 2 d/wk				2.4 (CEL: liver tumors)	Kashyap et al. 1979 technical

ALP = alkaline phosphatase; CEL = cancer effect level; d = day(s); F = female; Gn pig = guinea pig; GOT = glutamate oxaloacetate transaminase; GPT = glutamate pyruvate transaminase; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; NS = not specified; wk = week(s); x = time(s).

a 2-year-old boy exposed to a family dog that was dipped regularly in mange treatment containing 12% γ-HCH (Vodopick 1975).

No studies were located regarding hematological effects in animals following dermal exposure to any of the HCH isomers.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals following dermal exposure to HCH.

Hepatic Effects. No studies were located regarding hepatic effects in humans following dermal exposure to HCH.

Liver pathology, including dilation of sinusoids, focal fatty inclusions, hypertrophy of hepatocytes, thickened blood vessels, swelling, and proliferation of epithelial cells of bile ducts, was observed in guinea pigs treated with 100 mg technical-grade HCH/kg/day for 30 days (Dikshith et al. 1978). The patch of the abdomen on which the HCH was applied was not covered to prevent licking, so oral exposure may also have occurred. In rabbits exposed to 25 mg technical-grade HCH/kg/day for 30 days, there were degenerative changes in hepatocytes along with increased liver and serum GPT and alkaline phosphatase (Dikshith et al. 1989b). Liver cell hypertrophy, fatty degeneration, nuclear pyknosis, and focal and diffuse necrosis were found in female rats treated with 100 mg/kg/day technical-grade HCH for 7–30 days, but the time that it took for these lesions to occur, the severity, and the number of animals affected were not reported (Dikshith et al. 1991c). Centrilobular hypertrophy was reported in male and female rats exposed dermally to 60 mg lindane/kg/day for 13 weeks, 5 days/week, 6 hours/day (Brown 1988).

Renal Effects. No studies were located regarding renal effects in humans following dermal exposure to HCH.

Female rats treated with 100 mg/kg/day of technical-grade HCH for 7, 15, or 30 days had necrosis and atrophy of the renal tubules and glomeruli, although the number of animals affected and the severity of the lesions were not reported (Dikshith et al. 1991c). Similar effects were noted in male rabbits treated with 25 mg/kg/day technical-grade HCH (Dikshith et al. 1989b). Male rats treated dermally with 10 mg/kg/day lindane for 13 weeks exhibited hyaline droplet formation, and urinalysis showed increased cast formation and

positive scores for protein, blood, and turbidity in treated males (Brown 1988). Females in the same study exhibited a slight increase in the incidence of tubular basophilia at 60 mg/kg/day.

Dermal Effects. Rashes were observed in a boy following treatment with shampoo containing γ-HCH (Fagan 1981). No exposure level was reported, but the shampoo was rinsed over the boy's entire body.

Mild dermatitis was observed in rats after 15 skin paintings with 180 mg/kg/day γ-HCH/kg for 25 days (Dikshith et al. 1973). Rabbits exposed to 132 mg/kg moistened lindane for 4 hours showed no primary skin irritation or other toxic symptoms (Ullmann 1986d). Rabbits exposed to technical-grade HCH (25 mg/kg/day for 30 days) had hyperkeratinization of the epidermal layer and swollen collagen fibers in the dermis, but no scoring level was provided (Dikshith et al. 1989b). Dermal treatment of rats with 100 mg/kg/day technical-grade HCH for 7–30 days resulted in hyperkeratosis, epidermal cell vacuolization, and thickening of collagen fibers (Dikshith et al. 1991c).

Ocular Effects. No studies were located regarding ocular effects in humans following dermal exposure to HCH.

Mild eye irritation was seen in rabbits exposed to 26 mg/kg lindane in the conjunctival sac for up to 72 hours, giving a primary irritation score of 0.6 out of a maximum possible cumulative score of 16 (Ullmann 1986c).

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans or animals following dermal exposure to HCH.

2.2.3.4 Neurological Effects

There have been several reports of human intoxication involving convulsions in children after excessive topical application of γ-HCH (Lee and Groth 1977; Matsuoka 1981; Ramchander et al. 1991; Telch and Jarvis 1982; Tenenbein 1991); exposure levels were not reported. Heiberg and Wright (1955) reported convulsions in a woman who had treated calves with an insecticide containing 11% γ-HCH and 16% other HCH isomers. Weakness of the left and right limbs, dysarthria, and dysphagia were seen in an agricultural worker exposed by inhalation and dermal contact to unspecified levels of several organochlorine pesticides,

including lindane (Fonseca et al. 1993). A man with human immunodeficiency virus (HIV) exhibited generalized tonic-clonic seizure activity after a single topical application of a 1% lindane lotion to treat scabies (Solomon et al. 1995).

Studies in animals have substantiated the neurological symptoms resulting from γ-HCH application. Manifestations such as excitability, seizures, and convulsions have been observed in rabbits following a single topical application of 60 mg lindane/kg in a 1% solution (Hanig et al. 1976); young rabbits were more susceptible than older rabbits. Slight sedation was observed in rats exposed once for 24 hours to 1,000 mg/kg lindane through shaved dorsal skin (Ullmann 1986a). Sedation was severe in one female receiving the highest dose (2,000 mg/kg). This female also showed severe spasms. Damage to Purkinje cells in the cerebellum and tremors were found in female Wistar rats treated with 100 mg/kg/day technical-grade HCH for 7–30 days (Dikshith et al. 1991c). Aggressiveness or hyperactivity was noted in female rats exposed dermally for 13 weeks to 10 mg lindane/kg/day, while ataxia and tremors were seen at 60 mg/kg/day (Brown 1988).

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following dermal exposure to HCH. Dikshith et al. (1978) reported testicular hypertrophy and atrophy and complete inhibition of spermatogenesis in guinea pigs dermally treated with technical-grade HCH for 7, 15, or 30 days at doses as low as 100 mg/kg/day. The patch of the abdomen on which the HCH was applied was not covered to prevent licking, so oral exposure more than likely occurred. In a similar study, the backs of male rats were sprayed with 50 or 100 mg/kg/day technical-grade HCH for 120 days and the rats were housed in separate cages to prevent licking (Prasad et al. 1995). Depletion of germ cells and impaired function of Leydig and Sertoli cells was suggested by significant dose-related changes in activities of testicular enzymes such as sorbitol dehydrogenase, glucose-6-P-dehydrogenase, γ-glutamyl transpeptidase, and β-glucoronidase. Significant reductions in sperm count and motility and increased percentages of abnormal sperm were also observed in both groups. A significant reduction in testosterone level was observed in the high dose group.

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following dermal exposure to HCH.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following dermal exposure to HCH.

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

A case-control study surveying childhood brain cancer cases among Missouri residents found that the odds ratios for the use of Kwell, a shampoo containing lindane for lice control, were slightly elevated during the first 7 months of age to diagnosis (Davis et al. 1993). Thus, Kwell use was significantly associated with childhood brain cancer compared to controls. However, this study was limited by small sample sizes, potential recall bias in questionnaires, multiple comparisons, and the lack of detailed exposure information.

In mice, dermal exposure to a 0.5% solution of γ-HCH in acetone applied twice a day for 60 days was reported to result in no treatment-related tumors (Orr 1948). Increases that were not statistically significant were reported in the incidences of hyperplastic and preneoplastic areas in the liver and hepatic tumors in Swiss mice exposed to 2.4 mg technical-grade HCH/kg/day for 80 weeks (Kashyap et al. 1979). Limitations of these studies, including less-than-lifetime exposure and study duration, the testing of only one dose, and the potential for ingestion of some of the compound from the skin, preclude determination that dermally applied HCH is noncarcinogenic in mice.

2.3 TOXICOKINETICS

Absorption of the various HCH isomers following inhalation, oral, or dermal exposure has been inferred from humans who have become ill or who had increased serum levels of the various isomers following exposure by these routes. No animal data are available from the inhalation route to quantify the extent or rate of absorption. Technical-grade HCH has been shown to be well absorbed from the gastrointestinal tract of animals (Albro and Thomas 1974). The distribution of HCH isomers in humans and animals is primarily to the adipose tissue but also to the brain, kidney, muscle, blood, and other tissues (Siddiqui et al. 1981a; Baumann et al. 1980). β-HCH accumulates to a much greater extent than γ-HCH. The excretion of HCH isomer metabolites is primarily through the urine. The isomers have also been detected in breast milk (Ejobi et al.

1996; Schoula et al. 1996) and semen (Szymczynski et al. 1981) . The primary urinary metabolites are chlorophenols and an epoxide. The conversion occurs mainly by the action of hepatic enzymes.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Evidence exists that humans absorb γ-HCH vapor or dusts via inhalation. This can be inferred from occupational studies in which adverse health effects, including hematological abnormalities and neurological effects, have been reported in workers exposed to γ-HCH in workplace air (Brassow et al. 1981; Czegledi-Janko and Avar 1970; Kashyap 1986; Samuels and Milby 1971). In addition, α-, β-, γ-, and δ-HCH have been detected in the blood serum, adipose tissue, and semen of occupationally and environmentally exposed individuals indicating that absorption does take place (Baumann et al. 1980; Czegledi-Janko and Avar 1970; Kashyap 1986; Nigam et al. 1986; Saxena et al. 1980, 1981a, 1981b). There are no specific studies that have quantified the rate or extent of absorption of the HCH isomers following inhalation exposure. No information is available on the absorption of α-, β-, γ-, and δ-HCH following inhalation exposure in experimental animals.

2.3.1.2 Oral Exposure

In humans, HCH is absorbed following oral exposure. Many accidental poisonings have occurred in humans as a result of γ-HCH ingestion, and high blood concentrations have been demonstrated in a number of acute poisoning cases (Berry et al. 1987; Harris et al. 1969; Khare et al. 1977; Munk and Nantel 1977; Nantel et al. 1977; Powell 1980; Starr and Clifford 1972).

HCH is similarly absorbed following oral exposure in animals. Information concerning the rate of absorption from the gastrointestinal tract can be inferred from studies conducted in mice and rats. These studies indicated that γ-HCH is readily absorbed from the gastrointestinal tract (Ahdaya et al. 1981; Turner and Shanks 1980). Ahdaya et al. (1981) demonstrated that half of the administered dose was absorbed from the gastrointestinal tract of fasting mice approximately 14 minutes after administration of radiolabelled γ-HCH by stomach tube. Although this study demonstrates the rapid absorption of γ-HCH from the gastrointestinal tract, the use of fasted animals prevents an assessment of the effect of stomach contents on the rate of absorption. Turner and Shanks (1980) studied the rate of absorption of γ-HCH from the gastrointestinal

tract and intestinal lymphatic system using rat intestinal loop preparations. Prepared loops were injected with γ-HCH, and the blood and lymph were sampled for 30 minutes. γ-HCH was readily absorbed from the intestine into the blood; however, only a small amount of γ-HCH entered the lymphatic system from the intestine.

Absorption of technical-grade HCH following oral exposure has been quantified in rats. The extent of absorption of technical-grade HCH has been estimated to be 95.8% in rats within 4 days following the oral administration of single doses of the substance (Albro and Thomas 1974). Variation of the dosages from 30 to 125 mg/kg had no effect on the percentage of absorption. The overall degree of absorption of technical-grade HCH administered in the feed for 14 days was similar (94.9%), but the average absorption values of α-, β-, γ-, and δ-HCH were 97.4%, 90.7%, 99.4%, and 91.9%, respectively (Albro and Thomas 1974).

2.3.1.3 Dermal Exposure

The ready absorption of γ-HCH across human skin, due to its lipid solubility, has been demonstrated in several studies that examined the absorption of γ-HCH from an antiscabies lotion (Feldmann and Maibach 1974; Lange et al. 1981; Franz et al. 1996). Maximum serum levels in healthy volunteers and scabies patients were reported within 4–6 hours following whole-body application (Lange et al. 1981). However, the maximum serum levels of γ-HCH in scabies patients were greater than those reported for normal volunteers. Studies involving a single topical application of γ-HCH to the forearm, which was left for 24 hours before washing, indicate that at least 9% of the applied dose was absorbed; maximum absorption occurred during the first 12 hours after application of γ-HCH to the skin, but absorption continued for at least 5 days (Feldmann and Maibach 1974).

The absorption of γ-HCH through the skin was studied following application of 2 different preparations to the forearm of human volunteers (Dick et al. 1997a). One with 120 mg γ-HCH/ml in acetone as the vehicle and the other, a commercial product, consisted of 3 mg γ-HCH/ml formulation which primarily contained white spirit as the solvent base. The proportion of the applied dose absorbed into the systemic circulation in 6 hours was 5% for the dose applied in acetone and 60% of the applied dose in white spirit-based formulation. Thus, the white spirit enhanced the absorption of γ-HCH relative to acetone as the vehicle. The absorption of γ-HCH through human skin was also assessed in an *in vitro* study (Dick et al. 1997b). γ-HCH absorption was reported to be 15–25% in 24 hours for the 2 formulations that contained white spirit as the

predominant solvent, 3% in 24 hours from an aqueous spray dilution, and <1% in 24 hours for the acetone preparation.

γ-HCH is similarly absorbed through the skin of animals. Toxicity was observed in guinea pigs and rabbits following dermal exposure to γ-HCH and following dermal exposure to technical-grade HCH (Dikshith et al. 1978; Hanig et al. 1976). Male rats treated dermally with radiolabelled lindane (20% emulsifiable concentrate) on a 4.9 cm^2 shaved dorsal area exhibited absorption of radiolabel which increased with time of exposure (Bosch 1987a). After 4 hours, 10.1%, 5.3%, and 2.0% were absorbed from doses of 0.06, 0.6, and 6 $mg/cm^2/kg$, respectively. After 24 hours, 27.7%, 20.9%, and 5.1% were absorbed from doses of 0.06, 0.6, and 6 $mg/cm^2/kg$, respectively. Male rabbits treated dermally with radiolabelled lindane (20% emulsifiable concentrate) in a 28.3-cm^2 shaved dorsal area absorbed, after 4 hours, 29.6%, 18.3%, and 7.3% radiolabel from doses of 0.005, 0.05, and 0.5 $mg/cm^2/kg$, respectively, and, after 24 hours, 55.7%, 40.0%, and 16.6% from the same respective doses (Bosch 1987b).

The absorption of γ-HCH in infants and children who had received dermal treatment with 1% lindane(γ-HCH) lotion was investigated in one study (Ginsburg et al. 1977). Maximum blood concentrations were observed in 6 hours, and averaged at 0.028 μg/ml for the group infected with scabies and 0.024 μg/ml for the noninfected group.

2.3.2 Distribution

Placental transfer of HCH in humans has been well documented (Saxena et al. 1981a). The levels of HCH and other organochlorine insecticides were found to be higher in the maternal blood, placenta, and umbilical-cord blood of stillborn cases than those of live-born cases (Saxena and Siddiqui 1983). HCH has been shown to accumulate in amniotic fluid, placenta and fetal tissues after oral treatment of pregnant mice (Srivastava and Raizada 1993) and can be related to fetolethality. HCH isomers have been detected in human breast-milk, particularly in developing countries that still use HCH as a pesticide. Detected concentrations in these studies are discussed in Section 5.6. In a study on rats, γ-HCH has been reported to be transferred in the breastmilk and to elicit neurological effects in neonates. Epileptiform seizures have been reported in male rats fed maternal milk for 12 days beginning on the third day after birth, from dams exposed daily to 20 mg γ-HCH/kg by gavage (Albertson et al. 1985). In another study, lactating females were treated orally with a single dose of 6 mg/kg of γ-HCH on day 9 to 14 of lactation, the testosterone level of the male offspring was reduced 50% when puberty was reached (day 60) when compared to the control group (Dalsenter et al. 1997).

When the offspring reached adulthood (day 140 postnatal), the relative testicular weight was significantly lower (Dalsenter et al. 1997). The number of sperm and spermatids was also significantly reduced. α-, β-, and γ-HCH have been found to be bioconcentrated and excreted in women's breast milk who have been exposed to technical-grade HCH in pesticide residues (Nair et al. 1996).

2.3.2.1 Inhalation Exposure

Information on the distribution of the HCH isomers, following inhalation by humans, comes from studies of humans exposed to HCH in the workplace. Air concentrations of α-HCH (0.002–1.99 mg/m^3), β-HCH (0.001–0.38 mg/m^3), and γ-HCH (0.004–0.15 mg/m^3) were associated with concurrent mean blood serum levels in workers of 69.6, 190.3, and 36.9 µg/L, respectively (Baumann et al. 1980). Serum levels of total HCH of 0.14–0.60 ppm were found in workers with unknown levels of exposure to technical-grade HCH (Nigam et al. 1986). HCH isomers have also been detected in the adipose tissues of workers occupationally exposed and individuals exposed via the ambient environment (Baumann et al. 1980; Siddiqui et al. 1981a). Accumulation of β-HCH has been shown to increase approximately linearly with time of exposure (Baumann et al. 1980). Siddiqui et al. (1981a) found adipose levels of 0.1–1.5, 0.06–0.9, 0.7–3.0, and 0.97–5.8 ppm of α-, β-, γ-, and total HCH, respectively, in the tissues collected during an autopsy case study conducted in India.

In a study with Wistar rats exposed to air concentrations of 0.02–5 mg/m^3 lindane for 90 days, male rats exhibited higher serum lindane levels than females, but females had higher liver, brain, and fat levels (Oldiges et al. 1983). The organ levels of lindane were dose-dependent but had returned to baseline levels after a 4-week recovery period.

2.3.2.2 Oral Exposure

Information on the distribution of the HCH isomers following ingestion by humans comes from case reports. A fatal poisoning case confirmed that γ-HCH is, in part, distributed to the central nervous system. γ-HCH was detected in the cerebrospinal fluid of a young boy following ingestion of an unknown quantity of γ-HCH (Davies et al. 1983).

More detailed information on the distribution of HCH or its isomers is available from studies in which laboratory animals were exposed by ingestion (Chand and Ramachandran 1980; Eichler et al. 1983;

Srinivasan and Radhakrishnamurty 1983b). These studies examined the overall distribution pattern of HCH isomers. γ-HCH and β-HCH are primarily stored in the fat of rats acutely exposed for 5, 10, or 15 days (Srinivasan and Radhakrishnamurty 1983b). The overall distribution of γ-HCH was greatest in fat, followed by brain, kidney, muscle, lungs, heart, spleen, liver, and blood. More recently, γ-HCH has also been found in the adrenal glands of rats (Lahiri et al. 1990; Sulik et al. 1988). In an experiment lasting 12 days, the accumulation of γ-HCH in the brain of rats gavaged with 5 or 12 mg/kg/day began to decline after 8 days. This reduction was not observed in rats gavaged with 20 mg/kg/day (Tusell et al. 1988). In rats gavaged with γ-HCH on lactation day 9 or 14, γ-HCH levels were higher in their milk than plasma (Dalsenter et al. 1997). Levels of γ-HCH in the offspring of those rats were approximately twice as high in kidneys and liver than in brain and testes. In the brain of rats, α-HCH has been found to accumulate preferentially in the white matter, an area containing lipid-rich myelin, as opposed to gray matter (Portig et al. 1989). However, the same brain distribution pattern was not noted for γ-HCH in mice, despite the fact that it is equally lipophilic. Differences in distribution of γ-HCH and α-HCH are most likely due to stereospecific forces.

The distribution pattern for β-HCH was found to be in the following order: fat > kidney > lungs > liver > muscle > heart > spleen > brain > blood. For γ-HCH, the distribution pattern was as follows: fat > brain > kidney > muscle > lungs > heart > spleen > liver > blood. β-HCH accumulates in tissues to a greater degree than γ-HCH except in the brain, where the γ-HCH accumulates at a higher concentration (Srinivasan and Radhakrishnamurty 1983b). This accumulation increases with increasing dose and treatment period for β-HCH more so than for γ-HCH. The greater accumulation of β-HCH in tissues is expected since this isomer is known to be metabolized more slowly. In addition, γ-HCH is known to induce the liver mixed-function oxygenase system, and thus. self-induced metabolism is an important factor that minimizes the accumulation of γ-HCH residues in animal tissues.

The preferential accumulation of HCH in fatty tissues is also observed following intermediate-duration exposure of rats to HCH (isomer unspecified) in the diet (overall distribution: fat > liver > serum) (Chand and Ramachandran 1980) or exposure to α- or γ-HCH by gavage (overall distribution: fat > kidney > liver > brain > blood) (Eichler et al. 1983).

2.3.2.3 Dermal Exposure

Information on the distribution of the HCH isomers in exposed humans comes from case reports. A fatal poisoning case indicated that γ-HCH is, in part, distributed to the brain following topical application. The isomer was detected in brain tissue (110 ppb) and heart blood (33.3 ppb) collected during the autopsy of an infant who was treated with a whole-body application of a 1% γ-HCH lotion after a hot bath (Davies et al. 1983). In another study, blood levels of γ-HCH peaked 6 hours following topical application of a 1% solution to 20 children (12 infected with scabies, 8 noninfected) (Ginsburg et al. 1977). Mean concentrations did not differ statistically between the two groups at 6 hours and were 0.024 µg/ml in healthy children and 0.028 µg/ml in infected children. The half-life in blood was 17.9 hours and 21.4 hours in infected and healthy children respectively. Differences in dosage between the two groups of children were considered marginally significant (p=0.11). However, the infected children were younger. The mean age for the infected and noninfected group were 32.5 months and 64.3 months, respectively.

The distribution of γ-HCH through the skin was studied following application of 2 different preparations to the forearm of human volunteers (Dick et al. 1997a). The mean peak plasma concentrations of γ-HCH following exposure to the acetone and white-spirit based applications were 0.91 and 0.47 ng/mL, respectively; although the preparation in acetone contained a 40-fold higher concentration of γ-HCH. About 30% of the applied dose for the white-spirit based formulation was observed in the stratum corneum at 6 hours exposure and decreased by 90% at 24 hours. Fifteen percent of the applied dose for the acetone-based application was located in the stratum corneum.

Some information on the distribution of γ-HCH is available from studies in which laboratory animals were exposed by dermal application (Bosch 1987a, 1987b; Hanig et al. 1976; Solomon et al. 1977a, 1977b). A study on the distribution of γ-HCH in guinea pigs following acute dermal exposure indicates that accumulation of γ-HCH in the brain is greater than in the blood after single and multiple topical applications (Solomon et al. 1977a, 1977b); the levels in both tissues increased with the number of applications. Experiments with radiolabeled lindane in dermally treated rats (Bosch 1987a) and rabbits (Bosch 1987b) found that absorption of radiolabel increased with time of exposure, with greater absorption and subsequent excretion in the urine occurring at the lower treatment doses. In weanling rabbits, which appear to be more sensitive to lindane toxicity from dermal exposure than young adults, levels of lindane in the blood after a single application of a 1% solution (60 mg lindane/kg) were 1.67 and 2.48 µg/mL in 2 individuals that had been shaved and depilated, then stripped to remove the keratin layer (Hanig et al. 1976). In contrast, a blood level of only 0.67 µg/mL was seen in an individual that had only been shaved and depilated, indicating that absorption increases with loss of skin integrity.

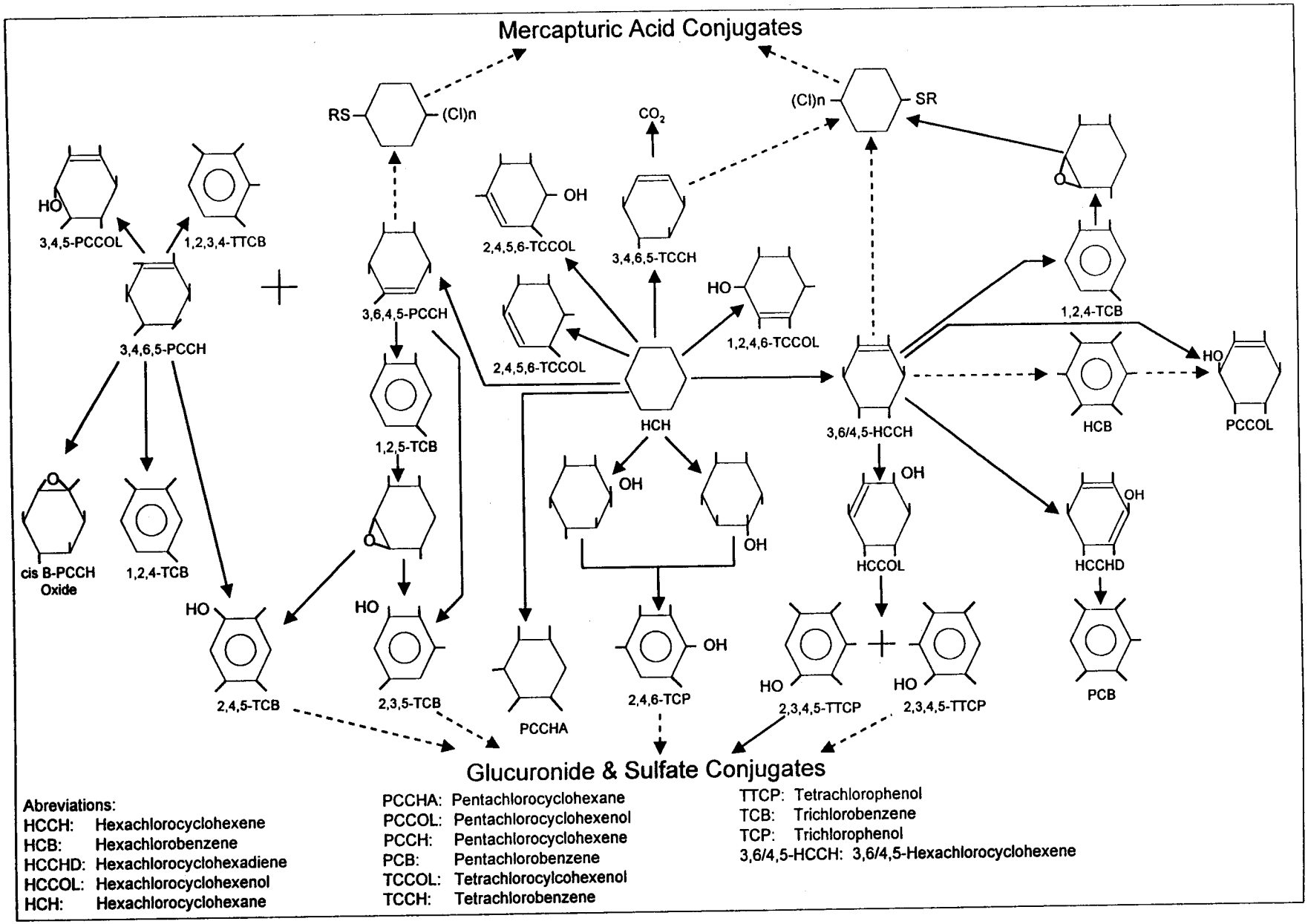
Following dermal treatment of rats with 50 or 100 mg/kg/day technical-grade HCH for 120 days, α-, β-, γ-, and δ-HCH were accumulated in testicular tissue and sperm in a dose-related manner (Prasad et al. 1995). β-HCH was present at the highest concentration in testicular tissue and sperm.

2.3.3 Metabolism

The metabolism of γ-HCH is illustrated in Figure 2-4. Angerer et al. (1983) determined that chlorophenols were the primary urinary metabolites of γ-HCH excreted by workers involved in γ-HCH production. In the study, glucuronides and sulfates of chlorophenols were cleaved by acidic hydrolysis of urine samples. The metabolites 2,3,5-, 2,4,6-, and 2,4,5-trichlorophenol accounted for almost 57.7% of the γ-HCH metabolites identified in the urine collected during the last 2 hours of the workers' shifts. Other urinary metabolites identified included other trichlorophenols, dichlorophenols, tetrachlorophenols, and dihydroxychlorobenzenes. Pentachlorophenol has also been identified as a urinary metabolite in humans following occupational exposure (Engst et al. 1979). *In vitro* investigations indicate that human liver microsomes convert γ-HCH by dechlorination, dehydrogenation, dehydrochlorination, and hydroxylation to 5 primary metabolites: 3,6/4,5-hexachlorocyclohexene, pentachlorocyclohexene, 2,4,6-trichlorophenol, 2,3,4,6-tetrachlorophenol, and pentachlorobenzene (Fitzloff et al. 1982). Similar *in vitro* studies have demonstrated that an epoxide forms during the metabolism of pentachlorocyclohexene. This stable halogenated hydrocarbon epoxide metabolite may be responsible for the mutagenic and carcinogenic effects of γ-HCH (Fitzloff and Pan 1984).

In animals, γ-HCH appears to be transformed by hepatic enzymes to form chlorophenols, chlorobenzene, chlorocyclohexanes, chlorocyclohexanols, and conjugates of mercapturic acid, glucuronide, and sulfate (Chadwick and Freal 1972a; Chadwick et al. 1978a; Engst et al. 1979; Kujawa et al. 1977). These metabolites have been identified in various tissues and in the urine of laboratory animals. Metabolites found in the liver of rats following intermediate exposure to γ-HCH via gavage or diet include di-, tri-, tetra-, and pentachlorobenzenes; pentachlorocyclohexenes; and pentachloro-2-cyclohexen-1-ol (Chadwick and Freal 1972a; Kujawa et al. 1977). Metabolites identified in the blood of these rats include di-, tri-, tetra-, and pentachlorophenols and pentachloro-2-cyclohexen-1-ol (Kujawa et al. 1977). Di-, tri-, and tetrachlorophenols; pentachlorocyclohexenes; and pentachloro-2-cyclohexen-1-ol have been identified in samples of kidney, spleen, heart, and brain tissue from rats fed γ-HCH (Kujawa et al. 1977). Metabolites found in the urine include tri-, tetra-, and pentachlorophenol; pentachloro-2-cyclohexen-1-ol; and isomers of tetrachloro-2-cyclohexen-1-ol (Chadwick and Freal 1972a; Chadwick et al. 1978c; Kujawa et al. 1977). The metabolism of γ-HCH in the intestine was reported to be very minor, or the metabolites were completely

Figure 2-4. The Proposed Metabolism of Hexachlorocyclohexane*



*Adapted from Chadwick et al. 1979, 1985; Fitzlof and Pan 1984; Fitzloff et al. 1982

absorbed. No metabolites were detected in the feces or in the adrenal gland (Kujawa et al. 1977). *In vitro* preparations using rat liver slices have also found that γ-HCH is converted to hexachlorobenzene (Gopalaswamy and Aiyar 1984). However, these findings have not yet been confirmed in *in vivo* experiments.

The major urinary metabolites formed in rats, following intermediate oral exposure to α- or β-HCH, were identified as tri- and tetrachlorophenols; pentachlorocyclohexene was also identified as a metabolite of γ-HCH in kidney tissue (Macholz et al. 1982a, 1982b).

The detoxification of γ-HCH appears to be dependent on the P-450 oxidative system. Intermediate exposure to lindane resulted in greater toxicity in DBA/2 (D2) mice than in C57BL/6 (B6) mice; the former are unresponsive to microsomal enzyme induction by lindane (Liu and Morgan 1986). Increased toxicity was associated with higher blood and brain concentrations in D2 mice than in B6 mice at the time of sacrifice. In addition, D2 mice were found to have more 2,4,6-trichlorophenol in the liver, kidney, and spleen than the less-susceptible B6 mice. The inability of D2 mice to undergo enzyme induction to increase the rate of detoxification led to γ-HCH's enhanced toxicity in this strain. Other investigators have demonstrated the importance of the hepatic microsomal enzymes in the detoxification of γ-HCH (Baker et al. 1985; Chadwick and Freal 1972a; Chand and Ramachandran 1980; Chadwick et al. 1981; Tanaka et al. 1979). Chadwick et al. (1981) demonstrated that pretreatment of rats with inducers of hepatic enzymes significantly influenced the metabolism and excretion of γ-HCH and its metabolites by altering specific metabolic pathways; excretion of γ-HCH metabolites in the urine increased nearly 4-fold following pretreatment with Aroclor 1254 or phenobarbitol. Following pretreatment with Aroclor 1254, a 7-fold increase in expired metabolites was observed. Naphthoflavon had no effect on excretion rate.

Metabolism of HCH has not been studied in children. However, although it is unknown whether the ability to metabolize HCH specifically differs between children and adults, some enzymes which belong to the enzyme superfamilies involved in phase II HCH metabolism are developmentally regulated in humans. The development of UDP-glucuronosyltransferase (responsible for glucuronide conjugation) depends on the enzyme isoform but in general adult activity is attained by 6–18 months of age (Leeder and Kearns 1997). Development of sulfotransferase (responsible for sulfate conjugates) activity is also substrate specific and is usually earlier than UDP-glucuronosyltransferase. In fact, levels of some sulfotransferases may be greater during infancy and early childhood than during adulthood (Leeder and Kearns 1997). A series of enzymes are involved in the production of mercapturic acid conjugates: γ-glutamyltranspeptidase, glutathione

S-transferase, cysteinyl glycinase, and N-acetyl transferase (Sipes and Gandolfi 1991). There are 2 superfamilies of N-acetyltransferases, and one—the N–acetyltransferase 2 superfamily—has members that are developmentally regulated in humans. There is some N-acetyltransferase 2 activity in fetuses by 16 weeks of gestation. Infants up to 2 months of age have the slow metabolizer phenotype (there is a genetic polymorphism in this enzyme in adults). The adult distribution of slow and fast metabolizer phenotypes is reached by 4–6 months of age and full adult activity is achieved at 1–3 years of age (Leeder and Kearns 1997).

2.3.4 Elimination and Excretion

Excretion of hexachlorocyclohexane has not been studied in children.

2.3.4.1 Inhalation Exposure

Humans excrete γ-HCH and its metabolites in urine, milk, and semen (Angerer et al. 1981). Chromatographic analysis of urine from humans occupationally exposed to HCH showed the presence of chlorinated phenols and all isomers of di-, tri-, and tetrachlorophenol (Angerer et al. 1981). In another study, the elimination of β-HCH was investigated in a group of 40 former workers of a γ-HCH-producing plant by analyzing at least 2 blood specimens from different time points between 1952 and 1980. The median half-life of β-HCH was 7.2 years, calculated by concentrations in whole blood, and 7.6 years, calculated by concentrations in extractable lipids (Jung et al. 1997), assuming first order kinetics for excretion. HCH is commonly detected in low concentrations (0.015 mg/kg fat) in the breastmilk of women exposed to HCH in the environment (Fytianos et al. 1985). All five of the HCH isomers discussed in this profile have been detected in human semen following environmental exposure, suggesting another route of elimination (Szymczynski and Waliszewski 1981). No animal studies using the inhalation route of exposure were located.

2.3.4.2 Oral Exposure

Excretion of γ-HCH and its metabolites in laboratory animals has been well documented. Data indicate that its major route of elimination is via the urine following intermediate and chronic oral feeding in mice (Chadwick et al. 1985). Very little is eliminated in exhaled air (Ahdaya et al. 1981; Chadwick et al. 1985) or

in feces (Chadwick et al. 1985) following acute, intermediate, and chronic oral administration in rodents. Because of its high lipid solubility, γ-HCH is excreted through the dam's milk (Dalsenter et al. 1997).

Very little γ-HCH is excreted unaltered. Various phenylmercapturic acid derivatives have been detected in the urine of rats, formed by the conjugation of γ-HCH metabolites with glutathione subsequent to dechlorinations and dehydrochlorinations (Allsup and Walsh 1982; Kurihara et al. 1979). *In vitro* investigations using rat liver cells indicate that β-HCH seems to resist, to some extent, conversion to the glutathione derivative; γ-HCH and α-HCH are readily conjugated (Fitzloff and Pan 1984; Fitzloff et al. 1982). γ-HCH derivatives are not only excreted in the form of phenylmercapturic acids; there is ample evidence that they are also excreted in the form of glucuronides and sulfate conjugates (Chadwick et al. 1978a).

2.3.4.3 Dermal Exposure

Nonmetabolized γ-HCH was excreted in the urine and feces of healthy volunteers and scabies patients acutely exposed to a 0.3% γ-HCH emulsion by whole-body application. The cumulative excretion of nonmetabolized γ-HCH was almost the same in the healthy volunteers and the scabies patients (Zesch et al. 1982).

The elimination of γ-HCH was studied following application of two different preparations to the forearm of human volunteers (Dick et al. 1997a). The elimination half-life was between 50–111 hours for the acetone-based application, and 25–58 hours for the white-spirit based formulation. Absorbed γ-HCH was excreted in the urine as conjugates of 2,4,6-; 2,3,5-; and 2,4,5-trichlorophenol. Only 0.01–0.15% of the dose was excreted in the urine in 72 hours following dermal exposure for 6 hours.

In a study in which children infected with scabies and their noninfected siblings were treated dermally with 1% lindane lotion, the blood level was found to diminish rapidly after application, with a half-life of 17.9 hours in infected children and 21.4 hours in noninfected children.

In male rats treated dermally with radiolabeled lindane, 0.28, 0.08, and 0.02% radiolabel were excreted in urine 4 hours after doses of 0.06, 0.6, and 6 mg/cm^2/kg, respectively (Bosch 1987a). After 24 hours, 4.4, 3.2, and 0.6% radiolabel were excreted in urine from the same respective doses. In a similar study with male rabbits, 3.8, 2.6, and 1.3% radiolabel were excreted in urine 4 hours after doses of 0.005, 0.05, and

0.5 mg/cm^2/kg, respectively (Bosch 1987b). After 24 hours, 25.5, 11.6, and 6.8% radiolabel were excreted in urine from the same respective doses.

2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically-sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-5 shows a conceptualized representation of a PBPK model.

If PBPK models for hexachlorocyclohexane exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

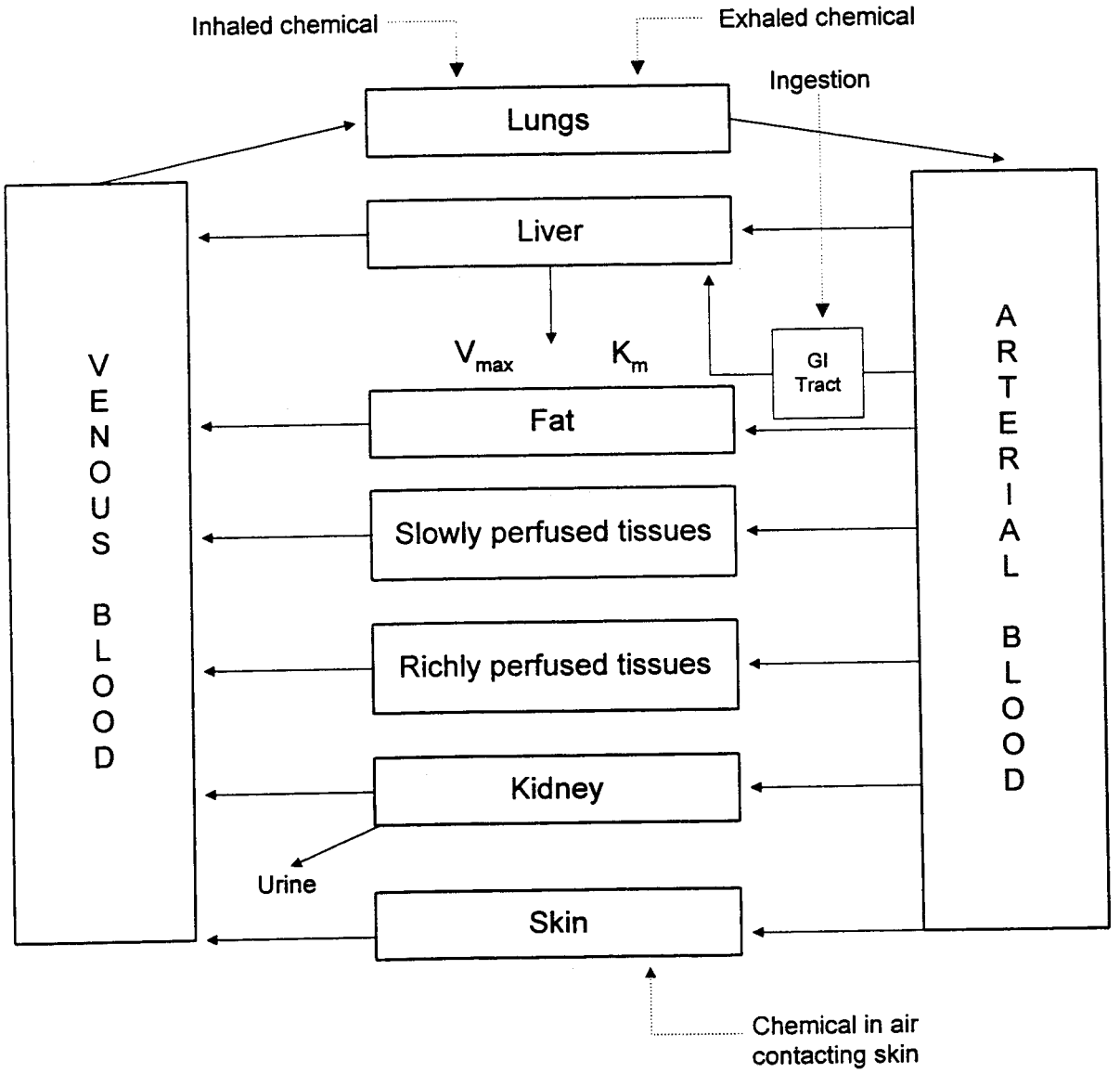
An existing PBPK model for hexachlorocyclohexane is discussed below.

2.3.5.1 Summary of PBPK Models.

DeJongh and Blaauboer (1997) simulated the kinetics of lindane in rats with a PBPK model. A five compartment model for the rat as presented in Figure 2-6 was constructed, including (1) the liver, serving as the metabolizing organ; (2) blood; (3) fat; (4) brain; and (5) a lumped compartment representing all other tissues, consisting mainly of muscle tissue. Values for the physiological parameters, tissue-blood partition coefficients, were obtained from the literature and are presented in Table 2-6. The model was calibrated on a dataset from the literature on the disposition of lindane from blood *in vivo* after single oral dosage and first order biotransformation and gastrointestinal absorption constants for lindane were obtained.

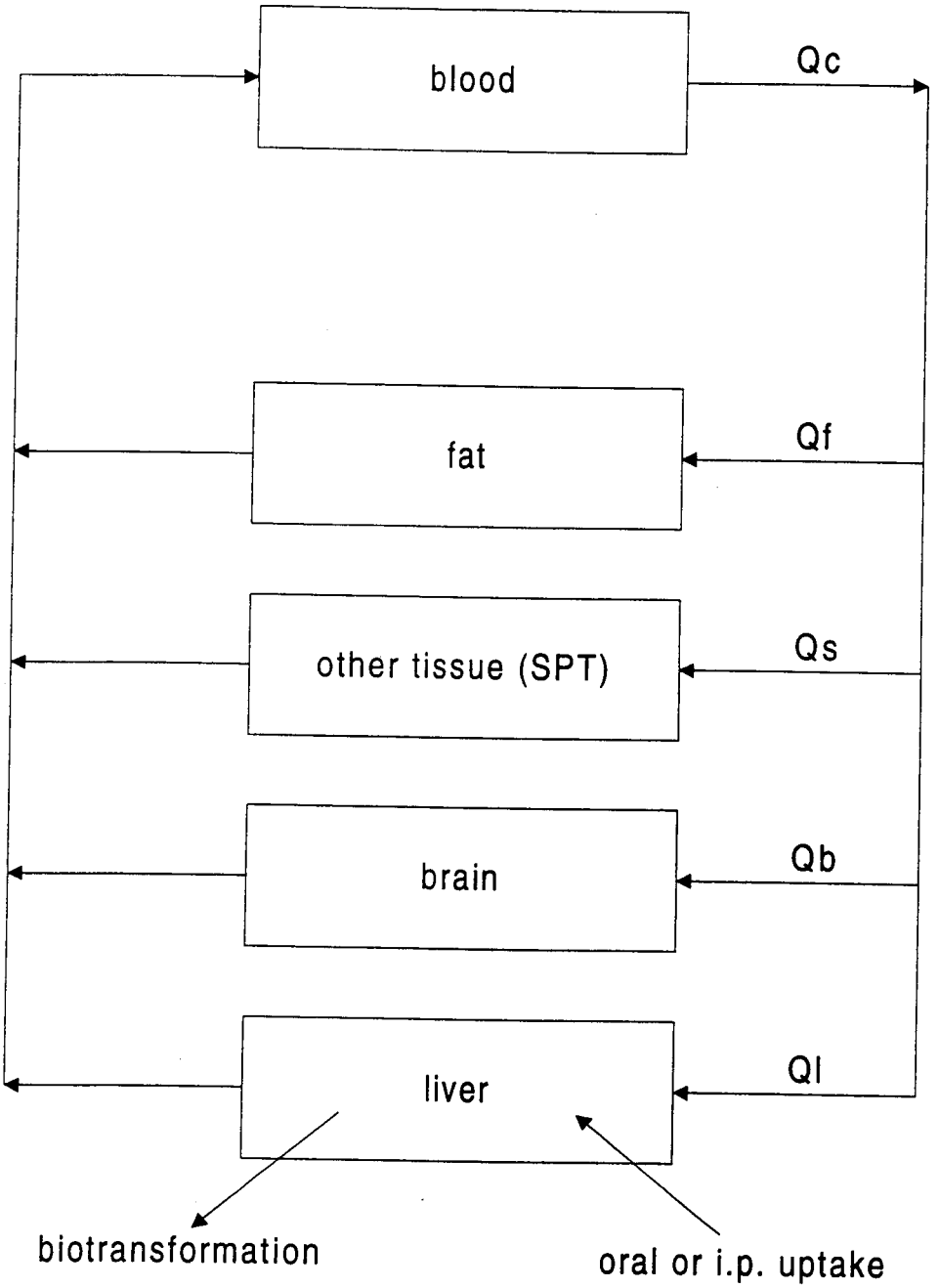
The model was validated by simulating the disposition of lindane *in vivo* after single intraperitoneal and chronic oral dosage and comparing simulated with experimental results. Simulated lindane concentrations in blood, brain, muscle, and fat after single intraperitoneal and chronic oral dosage compared adequately well with experimental results.

Figure 2-5. Conceptual Representation of a Physiologically-Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically -based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Figure 2-6. PBPK Model for Gamma-Hexachlorocyclohexane



Qc = movement from blood to other tissues
Qf = uptake to fat
Qs = uptake to other tissues
Qb = uptake to brain
Ql = uptake to liver

Table 2-6. Parameters for a PBPK Model for γ-Hexachlorocyclohexane in Rats

Parameter		Value	Scaling factor
Body weight (kg)		0.135-0.313	
—Cardiac output	(L/h kg)[a]	14	
$BW^{0.74}$			
Blood flow fractions[a]			
Liver		0.25	—
Fat		0.09	—
Other tissues (SPT)		0.63	—
Brain		0.03	—
Tissue group volume fractions			
Blood[a]		0.06	—
Liver[a]		0.04	—
Brain[a]		0.0006	—
Fat[b]		0.2 x BW + 0.0166	—
Remaining tissues (SPT)		0.894-VFC	—
Partition coefficients for toluene			
Liver-blood[c]		4.2	—
Fat-blood[c]		95.3	—
SPT-blood[c]		1.6	—
Brain-blood[d]		4.1	—
Metabolic and uptake constants			
Biotransformation rate[e]	(h^{-1} kg^{-1})	4.5	$BW^{-0.3}$
Oral/intraperitoneal uptake rate[e]	(h^{-1})	0.035	—
Oral/intraperitoneal uptake efficiency[d]		0.8	—

VFC, relative adipose tissue mass where VFC=0.2*BW + 0.0166
SPT, slowly perfused tissue.
[a] Reference values (Arms and Travis, 1988).
[b] Calculated as a function of body weight (Bailey et al., 1980).
[c] Measured *in vitro* (Jepson et al., 1994).
[d] Measured *in vivo* (Oshiba, 1972).
[e] Value obtained by calibration

There are no PBPK models for HCH in children.

Currently, ATSDR is assessing the feasibility of using tools such as physiologically based pharmacokinetic modeling and pharmacodynamic modeling to extrapolate data across routes or durations of exposure. ATSDR acknowledges that such extrapolation may be done on a substance-by-substance basis after adequate toxicokinetic information has been collected.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Information is available to assess the extent and rate of HCH absorption following oral and dermal exposure (Ahdaya et al. 1981; Albro and Thomas 1974; Turner and Shanks 1980). However, inhalation absorption of HCH can only be inferred from toxicity studies and studies assessing the distribution and excretion of γ-HCH. No quantitative information is available to assess the rate and extent of inhalation absorption. Additional data concerning the absorption of HCH in animals may provide information to assist in characterizing absorption of HCH in humans.

2.4.2 Mechanisms of Toxicity

In the nervous system, γ-HCH is thought to interfere with γ-aminobutyric acid (GABA) neurotransmitter function by interacting with the $GABA_A$ receptor-chloride channel complex at the picrotoxin binding site (Abalis et al. 1985; Anand et al. 1998; Casida and Lawrence 1985; Lawrence and Casida 1984; Pomès et al. 1994; Anand et al. 1998). Thus, the seizures caused by γ-HCH can be antagonized by $GABA_A$ mimetics. The δ-HCH isomer has also been shown to act at the picrotoxin binding site, but to a lesser extent (Fishman and Gianutsos 1988). In rat cortical neurons, expression of the protooncogene *c-fos*, which is associated with seizure activity and is induced by elevated intracellular calcium levels, was increased by γ-HCH treatment but decreased by δ-HCH treatment (Barrón et al. 1995). Treatment-related changes in *c-fos* expression suggested that γ-HCH induces seizures through the activation of calcium channels, while inhibition of calcium channels by δ-HCH results in anticonvulsant effects. The α-HCH isomer, another nonconvulsant, has been shown, like δ-HCH, to suppress c-*fos* induction (Vendrell et al. 1992a). In a study on the cytotoxic action of δ-HCH and γ-HCH in cultured rat cerebellar granule neurons (Rosa et al. 1997), both isomers were found to induce an increase in the free intracellular Ca^{2+} concentration. However, the γ-isomer mainly caused

this increase by a release from intracellular Ca^{2+} stores. On the other hand, δ-HCH may exert its action by stimulating a large influx of Ca^{2+}. δ-HCH was found to be more potent and active as a cytotoxic agent than γ-HCH, and the differences in cytotoxicity and neurotoxic action may be related to their action on the different Ca^{2+} pools. Other suggestive data concerning mechanisms by which HCH causes neurological effects in animals include enhanced synaptic activity (Joy 1982; Joy and Albertson 1985), altered GABA functional activity (Bhatt and Panchal 1994; Cattabeni et al. 1983; Fishman and Gianutsos 1987, 1988; Hulth et al. 1978; Joy and Albertson 1985), and inhibition of Na^{+}-K^{+}-ATPase (McNamara and Krop 1948a; Nakajima 1983; Uchida et al. 1974).

Lindane interacts with cellular membranes and may produce several generalized cytotoxic effects associated with impaired membrane function. In rat renal cortical tubules, glucose uptake and cyclic AMP accumulation were altered by lindane treatment (López-Aparicio et al. 1994). Transport of D-galactose and L-leucine across enterocytes was decreased in chickens injected daily with lindane for 7 days (Moreno et al. 1994). Rats exposed orally to 3.6 mg/kg/day technical-grade HCH for 3–6 months exhibited significantly decreased levels of phosphatidylinositol, phosphatidylinositol 4-phosphate, and phosphatidylinositol 4,5-bisphosphate in the erythrocyte membrane and cerebrum (Agrawal et al. 1995).

Oxidative stress in the liver has been suggested as a mechanism of γ-HCH-induced hepatotoxicity (Azzalis et al. 1995; Barros et al. 1988, 1991; Jungueira et al. 1993; Puri and Kohli 1995; Srinivasan and Radhakrishnamurty 1983a; Videla et al. 1991). This condition is characterized in the rat liver by a reduction in hepatic glutathione content, lipid peroxidation, the microsomal generation of superoxide radical coupled to cytochrome P-450 induction, and a decrement in superoxide dismutase and catalase activity (Jungueira et al. 1997). However, species differences exist in the activities of hepatic metabolizing enzymes, and it has been demonstrated that γ-HCH at a dose of 10 mg/kg/day for 6 days increased the hepatic cytochrome P-450 as well as glutathione-*S*-transferase in the rat, but not in the rabbit or monkey (Puri and Kohli 1995). Thus, oxidative stress and hepatotoxicity are produced with γ-HCH treatment in rats, but not in the rabbit and monkey (Puri and Kohli 1995). Inhibition of Mg^{2+}-ATPase activity has also been observed in rat liver tissue, suggesting an ATPase enzyme sensitivity to the action of γ-HCH (Gopalaswamy and Aiyar 1984). The researchers suggested that some toxic effects appearing in mammals as a result of γ-HCH exposure may arise from its influence on this ATPase activity (Gopalaswamy and Aiyar 1984).

Delayed vaginal opening and disrupted estrous cycle in female Fischer 344 rats and reduced embryo implantation in mice following γ-HCH treatment have been discussed as evidence of antiestrogenic activity

by γ-HCH(Chadwick et al. 1988; Cooper et al. 1989; Sircar and Lahiri 1989). This is in contrast to a previous study indicating estrogenic activity of γ-HCH based on increased glycogen content of the uterus, cervix, and vagina (Raizada et al. 1980). Also, in another study, β-HCH mobilized from fat during fasting produced estrogenic effects and stimulated growth of the uteri in ovariectomized mice (Bigsby et al. 1997). Inconsistencies in the classification of estrogenic activity for γ-HCH may have been due to variations in experimental protocols, examination of different endpoints, and controversy in the interpretation of hormonal effects (Chadwick et al. 1988).

2.4.3 Animal-to-Human Extrapolations

Extrapolating animal toxicity data to predict human risk from HCH exposure appears to be reasonable since similar effects are seen in both test subjects. However, caution must be exercised in animal-to-human extrapolation because of differences in metabolism, toxicokinetics, and mechanisms of toxicity.

Exceptions in extrapolation may include kidney damage in the male rat by γ-HCH (Dietrich and Swenberg 1990, 1991) via α-2μ-globulin, a protein that is not present in humans.

2.5 RELEVANCE TO PUBLIC HEALTH

Issues relevant to children are explicitly discussed in 2.6 Children's Susceptibility and 5.6 Exposures of Children.

Overview

Evidence was found in the reviewed literature that HCH isomers are toxic to humans and animals. Human exposure to HCH occurs primarily by occupational exposure, by ingesting HCH in contaminated food or water, or through the use or misuse of therapeutic lotions containing γ-HCH to control mites or lice. Humans are generally exposed to γ-HCH or to technical-grade HCH, which contains α-, β-, γ-, and δ-HCH. Technical-grade HCH and α-, β-, and δ-HCH isomers are currently unavailable in the United States; therefore, exposure to these isomers is likely to occur only in or near sites at which technical-grade HCH was disposed. Humans can absorb HCH following inhalation, ingestion, or dermal exposure. The possible human health effects associated with exposure to HCH are adverse hematological effects, hepatic effects, renal effects, immunological effects, neurological effects, reproductive effects, and cancer. These effects are

strongly dependent on dose, duration of exposure, route of administration, and the isomer to which the individual is exposed.

Minimal Risk Levels for α-, β-, γ-, and δ-HCH

Inhalation MRLs

No MRLs could be developed because of the lack of data.

Oral MRLs

- An MRL of 0.2 mg/kg/day has been derived for acute-duration (14 days or less) oral exposure to β-HCH. This was based on a NOAEL of 19 mg β-HCH/kg/day for neurotoxic effects (i.e., ataxia) in mice (Cornacoff et al. 1988). In this study, female B6C3F_1 mice were treated with β-HCH in the diet for 30 days. Mice receiving 57 or 190 mg/kg/day exhibited ataxia within 1 week. No ataxia was seen at 19 mg/kg/day.

- An MRL of 0.01 mg/kg/day has been derived for acute-duration oral exposure to γ-HCH. This was based on a NOAEL of 1 mg γ-HCH/kg/day for neurological (i.e., no increased kindling acquisition) effects in male rats (Joy et al. 1982). In this study, kindling (the development of seizure with repeated application of initially subthreshold electrical stimuli) was examined. Increased kindling acquisition was noted at 3 or 10 mg/kg/day dose levels but not at 1 mg/kg/day.

- An MRL of 0.0006 mg/kg/day has been derived for intermediate-duration oral exposure to β-HCH. This was based on a LOAEL of 0.18 mg β-HCH/kg/day for liver effects in rats (Van Velsen et al. 1986). In this study, hyalinization of centrilobular cells was observed at the low dose of 0.18 mg/kg/day. At 4.5 mg/kg/day (a higher dose), hepatic effects consisted of centrilobular hepatocytic hypertrophy, focal liver cell necrosis, and proliferation of smooth endoplasmic reticulum.

- An MRL of 0.00001 mg/kg/day has been derived for intermediate-duration oral exposure to γ-HCH. This was based on a LOAEL of 0.012 mg γ-HCH/kg/day for immunological/lymphoreticular effects in female mice (Meera et al. 1992). Effects consisted of a dose-dependent biphasic response, i.e.,

stimulation followed by suppression, in cell-mediated and humoral components of the immunological profile. A NOAEL for this effect was not established.

- An MRL of 0.008 mg/kg/day has been derived for chronic-duration (365 days and longer) oral exposure to α-HCH. This was based on a NOAEL of 0.8 mg/kg/day for liver effects in male and female rats (Fitzhugh et al. 1950). Hepatic effects at the 4 mg/kg/day dose level in this study included a significant increase in liver weight and slight microscopic liver damage, i.e., diffuse cell enlargement, focal necrosis, and fatty degeneration.

No acute-, intermediate-, or chronic-duration oral MRL's were derived for technical-grade HCH. HCH is not found in the environment as technical-grade HCH, and analytical methods do not detect or measure technical-grade HCH, but rather, the individual isomers. When technical-grade HCH is accidentally spilled into the environment, individual isomers partition into various media at different rates depending on the physical characteristics of each isomer. Some isomers may be more mobile in soil or water than others. Differences in partitioning and degradation would result in a different proportion of isomers than when initially spilled. Therefore, the development of an MRL for technical grade HCH would not be of value.

Death. Exposure to excessive amounts of HCH, primarily γ-HCH, by inhalation or ingestion, has been reported to result in death in humans (Loge 1965; Mobbs 1948; Storen 1955; Sunder Ram Rao et al. 1988). Doses of γ-HCH and β-HCH which have caused death in animals have been reported for acute oral and dermal exposures and intermediate-duration oral exposures. The acute lethality of HCH in animals may be related to its effects on the central nervous system since convulsions and coma were often observed prior to death. The doses associated with death and increased mortality in animals are much higher than would be caused by HCH in water or soil surrounding waste sites, so it is not likely that humans would die following brief or prolonged exposure to HCH in food, water, or soil.

Systemic Effects

Respiratory Effects. Mucous membrane irritation has been reported in humans exposed to a γ-HCH vaporizer (Conley 1952). Respiratory effects have not been reported in animal studies involving HCH inhalation (Klonne and Kintigh 1988; Oldiges et al. 1983). Whole-body, fatal, dermal exposure of an infant to 1% γ-HCH produced pulmonary petechiae (Davies et al. 1983). Rapid respiration or wheezing was seen in rats exposed dermally to 10 mg lindane/kg/day for 13 weeks (Brown 1988).

Cardiovascular Effects. Electrocardiogram abnormalities were seen in some workers exposed by inhalation to HCH (Kahyap 1986). Whole-body, fatal, dermal exposure of an infant to 1% γ-HCH produced epicardial petechiae (Davies et al. 1983).

Gastrointestinal Effects. Humans who ingested γ-HCH-contaminated food experienced vomiting, nausea, loss of appetite, and diarrhea (Nantel et al. 1977). Vomiting and diarrhea were also seen in a child dermally exposed to a 1% γ-HCH solution (Ramchander et al. 1991). Oral treatment with γ-HCH has inhibited enzyme activity in rat jejunum (Moreno et al. 1996).

Hematological Effects. Blood disorders, including anemia, leukopenia, leukocytosis, granulocytopenia, granulocytosis, eosinophilia, monocytosis, pancytopenia, and thrombocytopenia have been observed in individuals exposed to γ-HCH at work or in homes where HCH vaporizers were operated (Brassow et al. 1981; Danopoulos et al. 1953; Friberg and Martensson 1953; Gewin 1939; Jedlicka et al. 1958; Loge 1965; Mendeloff and Smith 1955; Morgan et al. 1980; Rugman and Cosstick 1990; Samuels and Milby 1971). Ingestion of γ-HCH has resulted in disseminated intravascular coagulation (Sunder Ram Rao et al. 1988). Dermal exposure to γ-HCH has resulted in anemia, bone marrow hyperplasia, and reduction of blood cell precursors in bone marrow (Rauch et al. 1990; Vodopick 1975; Woodliff et al. 1966). No significant hematological effects were reported in 40 workers exposed to γ-HCH in an occupational setting (Milby and Samuels 1971). There are no studies that examine hematological effects in animals following dermal exposure. Oral exposure to γ-HCH had no effect on hematological parameters in dogs and rats (Rivett et al. 1978; Suter 1983), but oral exposure in mice resulted in a reduction of bone marrow precursor cells (Hong and Boorman 1993). Oral exposure of rats to β-HCH resulted in reduced numbers of erythrocytes and leukocytes and decreased hemoglobin concentration and packed cell volumes (Van Velsen et al. 1986). Hematological effects were not observed in rats following inhalation exposure to γ-HCH (Oldiges et al. 1983). Ingestion of technical-grade HCH resulted in decreased white blood cell counts in rats (Joseph et al. 1992c).

Human data suggests that γ-HCH has the potential to induce adverse hematological effects but establishing a causal relationship has been difficult due to a lack of personal exposure data. Animals appear to be less sensitive to γ-HCH but comparison between humans and animals is difficult because limited data is available.

Musculoskeletal Effects. Seizures, limb muscle weakness, and necrosis were seen in humans who ingested γ-HCH powder (Munk and Nantel 1977; Sunder Ram Rao et al. 1988). Decreased cross-sectional bone area was seen in young rats treated with 20 mg/kg/day γ-HCH by gavage for 10 weeks (Andrews and Gray 1990). Suppression of marrow progenitor cells was seen in mice exposed to 10 mg/kg/day lindane for 10 days (Hong and Boorman 1993). In humans, severe poisoning with lindane can result in rhabdomyolysis (necrosis of skeletal muscle) with subsequent myoglobin release, resulting in secondary renal failure (Munk and Nantel 1977; Sunder Ram Rao et al. 1988).

Hepatic Effects. Hepatic effects, such as increased liver enzymes, have been reported in individuals exposed to technical-grade HCH principally by inhalation in a pesticide formulating plant (Kashyap 1986); there is no data reported for individuals who ingested HCH or applied γ-HCH to their skin. An increase in cytochrome P-450 concentration has been reported in rats following inhalation exposure (Oldiges et al. 1983). In animal experiments, ingestion of α-, β-, and γ-HCH and technical-grade HCH was reported to result in some degree of liver toxicity including increased microsomal activity, increased liver weight, mild-to-moderate liver necrosis and fatty degeneration, and liver cancer (Fitzhugh et al. 1950; Hanada et al. 1973; Ito et al. 1973, 1975, 1976; Kashyap et al. 1979; Munir et al. 1983; Nagasaki et al. 1975; NCI 1977; Oesch et al. 1982; Ortega et al. 1957; Thakore et al. 1981; Thorpe and Walker 1973; Tryphonas and Iverson 1983; Tsukada et al. 1979). Often, biochemical or gross changes were not accompanied by histopathological changes. Hepatic effects in animals, following dermal exposure to lindane and technical–grade HCH, were similar to those observed with oral exposure (Dikshith et al. 1978, 1989b, 1991c; Brown 1988). Available human studies are limited, but effects on liver enzymes following exposure to technical-grade HCH were similar to those observed in animal studies. The observation of serious hepatic effects in animals suggests that the same results could potentially occur in workers following prolonged occupational exposure.

Renal Effects. Evidence of renal dysfunction has not been observed in humans exposed to HCH by any route. However, renal effects including increased kidney weight, glucosuria, calcification, and nephritis have been reported in animals exposed to technical-grade HCH and α-, β-, γ-HCH in the diet (Fitzhugh et al. 1950; Srinivasan et al. 1984; Van Velsen et al. 1986). Studies from one laboratory (Dietrich and Swenberg 1990, 1991; Dikshith 1989a, 1991a; Philip et al. 1989a) indicate that the mechanism for renal toxicity of γ-HCH in Fischer-344 male rats may be based on rat α-2μ-globulin, a protein that does not occur in humans or female rats. However, female rats treated dermally with technical-grade HCH had demonstrated renal toxicity (Dikshith et al. 1991c). Thus, renal effects of HCH cannot be all attributed to α-2μ-globulin

interaction. However, at higher doses, lindane can produce lysis of the skeletal muscle with subsequent myoglobinuria, resulting in secondary kidney failure (Munk and Nantel 1977; Sunder Ram Rao et al. 1988).

Dermal Effects. The use of shampoo containing γ-HCH has resulted in skin rashes in humans (Fagan 1981). Dermatitis was seen in rats after daily skin paintings with 180 mg γ-HCH/kg/day for 15–25 days (Dikshith et al. 1973). Rabbits exposed to technical-grade HCH (25 mg/kg/day for 30 days) had hyperkeratinization of the epidermal layer and swollen collagen fibers in the dermis (Dikshith et al. 1989b). However, rabbits exposed to 132 mg/kg moistened lindane for 4 hours showed no primary skin irritation or other toxic symptoms (Ullmann 1986d).

Ocular Effects. Mice exposed to lindane aerosol (5 mg/m^3) for 14 weeks exhibited no ophthalmic effects (Klonne and Kintigh 1988). Mild eye irritation was seen in rabbits exposed to 26 mg/kg lindane in the conjunctival sac for up to 72 hours (Ullmann 1986c). No ophthalmoscopic effects were seen in rats exposed dermally to lindane (up to 400 mg/kg/day) for 13 weeks (Brown 1988).

Body Weight Effects. No effects on body weight in humans exposed to HCH by any route have been seen. No body weight effects were seen in rats exposed to up to 5 mg/m^3 lindane aerosol for 90 days (Oldiges et al. 1983). Significantly decreased body weight gain has been seen in rats treated orally with α- (Fitzhugh et al. 1950), β- (Fitzhugh et al. 1950; Van Velsen et al. 1986), γ- (Fitzhugh et al. 1950; Laws et al. 1994), and technical-grade HCH (Gautam et al. 1989; Joseph et al. 1992b; Nagaraja and Desiraju 1994).

Metabolic Effects. No metabolic effects in humans exposed to HCH by any route have been seen. Increased phosphoinositide turnover and generation of second messengers from phosphoinositides were seen in erythrocyte membranes from female rats treated by gavage with a single dose of 100 mg/kg technical-grade HCH, or with doses of 5 mg/kg/day technical-grade HCH for 3–6 months, 5 days/week (Agrawal et al. 1995). The latter exposure regime also resulted in a significant decrease in phosphatidylinositol, phosphatidylinositol 4-phosphate, and phosphatidylinositol 4,5-bisphosphate in erythrocyte membrane and cerebrum, and levels decreased with increased time of treatment (3–6 months).

Other Systemic Effects. No other systemic effects have been observed in humans or animals exposed to HCH by any route.

Immunological and Lymphoreticular Effects. A significant increase in the level of IgM was observed in workers exposed to technical-grade HCH (Kashyap 1986). Although there is no evidence of an increase in immunoglobulins in animals, antibody response has been reported to be depressed in rats, rabbits, and mice exposed to γ-HCH (Banerjee et al. 1996; Desi et al. 1978; Dewan et al. 1980). Biphasic effects on immunosuppression were reported in mice fed γ-HCH (Meera et al. 1992). This is suggestive evidence that HCH may affect the human immune system.

Neurological Effects. In humans, neurological effects including paresthesia of the face and extremities, headaches, vertigo, abnormal EEG patterns, and often seizures and convulsions have been reported in individuals occupationally exposed to γ-HCH or in individuals exposed accidentally or intentionally to large amounts of γ-HCH by ingestion or dermal application (Czegledi-Janko and Avar 1970; Davies et al. 1983; Harris et al. 1969; Heiberg and Wright 1955; Kashyap 1986; Lee and Groth 1977; Matsuoka 1981; Munk and Nantel 1977; Nantel et al. 1977; Powell 1980; Ramchander et al. 1991; Solomon et al. 1995; Starr and Clifford 1972; Telch and Jarvis 1982; Tenebein 1991). Acute- and intermediate-duration exposure of animals to high oral or dermal doses of γ- or β-HCH affects the central nervous system as evidenced by behavior disorders, decreased nerve velocity, convulsions, seizures, and coma (Albertson et al. 1985; Desi 1974; Dikshith et al. 1991c; Hanig et al. 1976; Muller et al. 1981; Tilson et al. 1987; Tusell et al. 1987; Van Velsen et al. 1986; Vendrell et al. 1992a, 1992b; Woolley and Griffith 1989). No histological examinations were conducted on the brain or nervous system of animals exposed by any route for any duration. The effects in humans and in animals suggest that exposure of humans to high air concentrations or large oral doses could result in neurotoxic effects.

Reproductive Effects. Alterations in reproductive hormones and increased blood levels of γ-HCH and total-HCH isomers have been detected in women that have undergone spontaneous abortion and premature delivery and have been reported in men occupationally exposed to γ-HCH and total-HCH isomers as well as to other organochlorine pesticides (Saxena et al. 1981a; Tomczak et al. 1981; Wasserman et al. 1982). The results of the Saxena et al. (1980, 1981a) studies suggest that pregnant women exposed to organochlorine pesticides, including γ-HCH, were at a greater risk for premature labor and/or abortion. The biological significance of altered hormonal levels in humans is difficult to assess, although the data do suggest that HCH may potentially affect reproductive capability. Similar reproductive hormonal effects have not been reported in animals. However, histological effects on the testes and uterus have been observed in rats orally exposed to high doses of β-HCH, γ-HCH, or technical-grade HCH (Dalsenter et al. 1996; Nigam et al. 1979;

Prasad et al. 1995; Raizada et al. 1980; Van Velsen et al. 1986) and in male rats fed milk from γ-HCH-treated dams (Dalsenter et al. 1997).

Although exposure by injection of γ-HCH in humans is unlikely, reproductive effects have been observed in animals exposed to γ-HCH by this route. Female rats exhibited decreased sexual receptivity after exposure to a 33 mg/kg intraperitoneal injection (Uphouse 1987). In addition, testicular changes including decreased organ weight and degeneration of tubules were observed after 10 daily exposures to 4 mg/kg intraperitoneal injections (Roy Chowdhury et al. 1987). Finally, 10 mg/kg intratesticular injections for 10 days resulted in hypertrophic or atrophic changes (Dikshith and Datta 1972). A three-generation feeding study in rats revealed no adverse reproductive effects from daily doses of approximately 10 mg/kg (Palmer et al. 1978a).

Developmental Effects. Although there are no data regarding developmental effects in humans via any route of exposure, there are animal data on developmental effects. A dose of 30 mg/kg γ-HCH administered to mice on day 12 of gestation caused decreases in fetal weight, fetal thymic weight, and placental weight (Hassoun and Stohs 1996a). The only consistent finding is for extra ribs, which is considered a normal variation and not a toxic effect (Palmer 1978a). However, dams that were exposed to 20 mg/kg/day β-HCH had pups that died within 5 days of birth (Srinivasan et al. 1991a). γ- and technical-grade HCH have altered neurotransmitter levels in rat offsprings (Rivera et al. 1991; Nagaraja and Desiraju 1994).

Genotoxic Effects. The available genotoxicity data indicate that γ-HCH and its individual isomers have some genotoxic potential, but the evidence for this is not conclusive.

γ-HCH has been tested in several *in vitro* genotoxicity studies. In bacteria, it was not observed to induce gene mutations in assays with or without a metabolic activation system (Moriya et al. 1983; Nagy et al. 1975), and it did not produce DNA damage, although a mammalian metabolic activation system was not present (Shirasu et al. 1976). γ-HCH was also not mutagenic in yeast (Shahin and von Borstel 1977) or algae (Kar and Singh 1979a). Mitotic disturbances (c-mitosis which is characterized by spindle breakdown as that produced by colchicine) and chromosome aberrations were observed in onion root tip cells exposed to commercial γ-HCH (Nybom and Knutsson 1947). In mammalian cells, γ-HCH (purity not reported) induced a marginal increase in the frequency of chromosome aberrations (including chromosomal gaps) in Chinese hamster cells, which was interpreted by the authors of the study as providing suggestive, but not conclusive, evidence of an effect (Ishidate and Odashima 1977). γ-HCH (NTP 1984) and technical-grade lindane (Murli 1990) were both reported to be negative for cytogenetic effects in Chinese hamster ovary cells. Technical-

grade lindane was also found inactive for inducing unscheduled DNA synthesis in rat primary hepatocytes *in vitro* (Cifone 1990). α-HCH and γ-HCH were reported to bind to calf thymus DNA in the presence of metabolic activation (Iverson et al. 1984). Cultured human lymphocytes taken from three healthy males showed a dose-dependent increase in chromosomal aberrations (gaps, breaks, and fragments) with significant increases at 0.1 µL/mL technical-grade HCH (6.5% γ-HCH) for 48-hour treatment and at 0.05 and 0.1 µL/mL for 72-hour treatment (Rupa et al. 1989d). In addition, sister chromatid exchanges increased in a dose-dependent manner with the high dose (0.1 µL/mL) producing the only significant result. These results suggest mild mutagenic activity at high doses in humans (Rupa et al. 1989d).

γ-HCH has also been tested *in vivo* in animals. Technical-grade HCH was reported to induce dominant lethal mutations in mice (Lakkad et al. 1982). It did not induce chromosome aberrations in bone marrow cells of Syrian hamsters (Dzwonkowska and Hubner 1986), but positive results were reported in bone marrow cells of rats exposed to β-HCH (Shimazu et al. 1972). γ-HCH was negative in a micronucleus assay in mice (Jenssen and Ramel 1980). α-HCH increased the mitotic rate and frequency of polyploid cells in rat hepatocytes (Hitachi et al. 1975). α-HCH produces DNA fragmentation in primary cultures of rat and human hepatocytes, but not in mouse hepatocytes (Mattioli et al. 1996). DNA repair induction was absent in hepatocytes from all three species. Both α- and γ-HCH have been observed to bind to mouse liver DNA at a low rate (Iverson et al. 1984).

Tables 2-7 and 2-8 present the results of *in vivo* and *in vitro* genotoxicity studies on γ-HCH.

Cancer. Use of γ-HCH pesticides by farmers was associated with a 50% increased risk of non-Hodgkin's lymphoma (Blair et al. 1998). However, a causal relationship could not be determined due to confounding effects such as use of other pesticides. With oral exposure, α-HCH, β-HCH, γ-HCH, and technical-grade HCH have been found to be carcinogenic in mice following long-term exposure (Hanada et al. 1973; Ito et al. 1973, 1975, 1976; Kashyap et al. 1979; Munir et al. 1983; Nagasaki et al. 1975; NCI 1977; Thakore et al. 1981; Thorpe and Walker 1973; Tsukada et al. 1979; Wolff et al. 1987). Hepatocellular carcinoma is the most frequently reported tumor type, although in many studies the liver was the only organ under investigation. In general, mice appear to be more susceptible to the carcinogenic effects of HCH isomers; rats generally developed cancer following longer exposure or exposure to higher doses. In addition, Schroter et al. (1987) reported that α-, β-, and γ-HCH promoted tumor development in rats exposed to a single dose of *N*-nitroso-morpholine. The available animal data suggest that liver cancer may be of potential concern to individuals exposed to HCH isomers for prolonged periods of time.

TABLE 2-7. Genotoxicity of Hexachlorocyclohexane Isomers *In Vivo*

Species (test system)	End point	Results	Isomer	Reference
Mammalian cells:				
Human (peripheral lymphocytes)	Chromosomal aberrations	-	Gamma	Kiraly et al. 1979
Syrian hamster (bone marrow)	Chromosomal aberrations	-	Gamma	Dzwonkowska and Hubner 1986
Rat (bone marrow)	Chromosomal aberrations	+	Beta	Shimazu et al. 1972
Mouse (germ cells)	Dominant Lethal	+	Technical	Lakkad et al. 1982
Mouse	Micronuclei	-	Gamma	Jenssen and Ramal 1980
Mouse (bone marrow)	Chromosomal aberrations	+	Gamma	Kumar et al. 1995
Mouse (liver)	DNA binding	(+)	Alpha/Gamma	Iverson et al. 1984
Rat (liver)	Mitotic disturbances	+	Alpha	Hitachi et al. 1975

+ = positive result; - = negative result; (+) = weakly positive result; DNA = deoxyribonucleic acid

TABLE 2-8. Genotoxicity of Hexachlorocyclohexane Isomers *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Isomer	Reference
Prokaryotic organisms:					
Salmonella typhimurium (TA100, TA98, TA1535, TA1537, TA1538)	Gene mutation	-	-	Gamma	Moriya et al. 1983
Escherichia coli (WP2/spot test)	Gene mutation	NT	-	Gamma	Nagy et al. 1975
E. coli (WP2 *hcr*)	Gene mutation	-	-	Gamma	Moriya et al. 1983
Bacillus subtilis (rec⁻ assay)	DNA damage	NT	-	Gamma	Shirasu et al. 1976
Eukaryotic organisms:					
Fungi and plant cells:					
Saccharomyces cerevisiae	Gene mutation	-	-	Gamma	Shahin and von Borstel 1977
Nostoc muscorum	Gene mutation	NT	-	Gamma	Kar and Singh 1979a
Allium cepa	Mitotic disturbances	NT	+	Gamma	Nybom and Knutsson 1947
Mammalian cells:					
Human (SV-40 fibroblasts)	Unscheduled DNA synthesis	-	-	Gamma	Ahmed et al. 1977
Human (peripheral lymphocytes)	Unscheduled DNA synthesis	NT	+	Gamma	Rocchi et al. 1980
Human (peripheral lymphocytes)	Sister chromatid exchange	NT	+	Technical	Rupa et al. 1989d
Human (peripheral lymphocytes	Chromosomal aberrations	NT	+	Technical	Rupa et al. 1989d
Chinese hamster (CHL cells)	Chromosomal aberrations	NT	(+)	Gamma	Ishidate and Odashima 1977
Calf (thymus DNA)	DNA binding	(+)	NT	Alpha/Gamma	Iverson et al. 1984

+ = positive result; - = negative result; NT = not tested; (+) = weakly positive result; DNA = deoxyribonucleic acid

A metabolite of γ-HCH, 2,4,6-trichlorophenol, accounts for 10–20% of γ-HCH-derived excretion products and may be responsible for some or all of the carcinogenic activity observed in mice. 2,4,6-Trichlorophenol has been classified by EPA as a group B2 compound based on evidence of its carcinogenicity in animal test systems (IRIS 1993). Similarly, a stable halogenated epoxide of the γ-HCH metabolite, pentachlorocyclohexene, may be responsible for the carcinogenic effects of γ-HCH (Fitzloff and Pan 1984). Pentachlorocyclohexene has been identified in the liver of rats exposed to γ-HCH (Chadwick and Freal 1972a; Engst et al. 1976; Kujawa et al. 1977). *In vitro* investigations indicate that human liver microsomal enzymes can convert γ-HCH to pentachlorocyclohexene and ultimately to the epoxide (Fitzloff et al. 1982).

2.6 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate due to maternal exposure during gestation and lactation. Relevant animal and in vitro models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in section 5.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both pre-natal and post-natal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Widdowson and Dickerson

1964; Foman et al. 1982; Owen and Brozek 1966; Altman and Dittmer 1974; Foman 1966). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns and at various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults and sometimes unique enzymes may exist at particular developmental stages (Leeder and Kearns 1997; Komori 1990; Vieira et al. 1996; NRC 1993). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in the newborn who has a low glomerular filtration rate and has not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; West et al. 1948; NRC 1993). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

Limited information is available on the specific health effects resulting from HCH exposure in children. Generally, health effects observed in adults should also be of potential concern in children. Occasional deaths of children have been reported following ingestion of γ-HCH (Storen 1955). Although a causal relationship between exposure to γ-HCH and hematological effects in humans has not been established, there is one case report of hypochromic anemia and another of aplastic anemia in children exposed to γ-HCH by inhalation (Morgan et al. 1980; Rugman and Cosstick 1990). There are also sporadic reports of adverse effects of γ-HCH including convulsions in children after excessive topical application of γ-HCH (Lee and Groth 1977; Matsuope 1981; Ramchander et al. 1991; Telch and Jarvis 1982; Tenebien 1991). Neurological effects have been observed in immature animals exposed to γ-HCH. Weanling rabbits were more sensitive to lindane (γ-HCH) than young adults, as seen by increased mortality rates accompanied by excitement and convulsions after a single whole-body treatment with a 1% solution (60 mg lindane/kg) that was absorbed dermally (Hanig et al. 1976).

Alterations in cerebral levels of noradrenaline, serotonin, and dopamine were observed in rats treated intragastrically with a single dose of 20 mg/kg γ-HCH during the postnatal period (Rivera et al. 1991). Levels of noradrenalin were reduced in the mesencephalon. Concentrations of a serotonin metabolite were increased in the frontal cortex primarily on postnatal days 8 and 15 , but the results were not statistically significant. Levels of a dopamine metabolite were decreased in the mesencephalon, but statistical significance was only obtained on postnatal day 15 (+44%, $p<0.05$). According to the authors, earlier experiments demonstrated that higher doses of γ-HCH were required to increase serotonin in adult rats. Alterations in levels of brain dopamine, serotonin, gamma-aminobutyric acid (GABA), glutamate, glutamate decarboxylase, and noradrenaline were seen in various areas of the brains of female rat pups treated orally with 10 mg technical-grade HCH/kg/day for 60 days (Nagaraja and Desiraju 1994). Epileptiform seizures have been reported in male rats fed maternal milk for 12 days, 3 days after birth, from dams exposed to 20 mg γ-HCH/kg by gavage (Albertson et al. 1985).

No direct information is available regarding the effects of HCH on the developmental process in humans. However, developmental studies in animals indicated few effects from exposure to γ-HCH (Khera et al. 1979; Hassoun and Stohs 1996a; Srinivasan et al. 1991a); significant teratogenic effects were not observed (Khera et al. 1978). The proportion of embryos lost after implantation was increased after minks were treated with 1 mg/kg/day γ-HCH in their diet (Beard et al. 1997). An increase in the incidence of fetuses with extra ribs was reported in rats exposed to 20 mg/kg/day γ-HCH during gestation days 6-15 and in rabbits exposed during days 6–18 (Palmer et al. 1978a). However, the incidence of extra ribs within or just greater than the ranges recorded for the control groups, and therefore, may not be significant evidence of teratogenicity caused by exposure to γ-HCH (Hassoun and Stohs 1996a). β-HCH given to rat dams at 20 mg/kg/day during gestation caused increased fetal deaths within 5 days of birth (Srinivasan et al. 1991a). In another study, cadmium interacted with γ-HCH to cause significant embryotoxic and teratogenic effects in the developing rat fetus when administered together at a dosage that for either toxin alone is insufficient to cause any deleterious effects in development (Saxena et al. 1986).

β-HCH is lipophilic and accumulates in maternal adipose tissue and may be mobilized during pregnancy and lactation. HCH residues have been measured in human skin lipids (Dua et al. 1998) and in breastmilk (Dua et al. 1997; Czaja et al. 1997; Nair et al. 1996); HCH also crosses the placenta (Saxena et al. 1981). Its levels in placenta, maternal blood, and umbilical-cord blood were higher in cases of stillbirths than in live-born cases; however, many other organochlorine pesticides were present that could have contributed to stillbirths (Saxena et al. 1983). In a study in rats, γ-HCH has been reported to be transferred in the maternal milk and

to elicit neurological effects in neonates. Following intraperitoneal dosing of dams with γ-HCH on days 12–17 of gestation, $GABA_A$ receptors in rat fetuses were studied with radiolabeled t-butylbicyclophosphorothionate (TBPS), a ligand that binds to the $GABA_A$ receptor (Brannen et al 1998). Treatment with γ-HCH significantly reduced the TBPS binding affinity in fetal brainstems and it was concluded that the effect could potentially lead to abnormal brain activity, increased susceptibility to seizures, and behavioral effects. Also noted in the study, was reduced TBPS binding in brains of fetuses when compared to adults. In another study, lactating female rats were treated orally with a single dose of 6 mg/kg of γ-HCH on day 9 or 14, or 1 mg/kg on days 9–14 of lactation; the testosterone level of the male offspring was reduced 50% at puberty (day 60) when compared to the control group (Dalsenter et al. 1997a). When the offspring reached adulthood (day 140 postnatal), the relative testicular weight was significantly lower (Dalsenter et al. 1997). The number of sperm and spermatids was also significantly reduced.

Differences in oxidative effects have been observed in the testes of young versus mature rats, 15 and 90 days old respectively, following intrapertitoneal injection with 10 or 20 mg/kg technical-grade HCH (Samanta and Chainey 1997). Lipid peroxidation occurred to a greater extent in mature rats. However, the percent decrease in cytosolic superoxide dismutase activity was greater in young rats, which have increased baseline activity of the enzyme. Based on the findings of this study, it does not appear that young rats are at increased risk of oxidative testicular damage.

Although it is unknown whether the ability to metabolize HCH specifically differs between children and adults, some enzymes, which belong to the enzyme superfamilies involved in phase II HCH metabolism, are developmentally regulated in humans. The development of UDP-glucuronosyltransferase (responsible for glucuronide conjugation) depends on the enzyme isoform, but, in general, adult activity is attained by 6–18 months of age (Leeder and Kearns 1997). Development of sulfotransferase (responsible for sulfate conjugates) activity is also substrate specific and is usually earlier than UDP-glucuronosyltransferase. In fact, levels of some sulfotransferases may be greater during infancy and early childhood than during adulthood (Leeder and Kearns 1997). A series of enzymes are involved in the production of mercapturic acid conjugates: γ-glutamyltranspeptidase, glutathione S-transferase, cysteinyl glycinase, and N-acetyl transferase (Sipes and Gandolfi 1991). There are two superfamilies of N-acetyltransferase, and the N-acetyltransferase 2 superfamily has members that are developmentally regulated in humans. There is some N-acetyltransferase 2 activity in fetuses by 16 weeks of gestation. Infants up to 2 months of age have the slow metabolizer phenotype (there is a genetic polymorphism in this enzyme in adults). The adult

distribution of slow and fast metabolizer phenotypes is reached by 4–6 months of age and full adult activity is achieved at 1–3 years of age (Leeder and Kearns 1997).

2.7 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to hydrogen sulfide are discussed in Section 2.7.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by hydrogen sulfide are discussed in Section 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.9, Populations That Are Unusually Susceptible.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to Hexachlorocyclohexane

There are few quantitative data to correlate levels of any of the HCH isomers in human tissue or fluids with environmental levels. A study in which children infected with scabies and their noninfected siblings were treated dermally with 1% lindane lotion found no correlation between the dose applied and the subsequent level of lindane in blood (Ginsburg et al. 1977). The blood level was also seen to diminish rapidly after application, with a half-life of 17.9 hours in infected children and 21.4 hours in noninfected children.

In contrast, β-HCH persists in the blood for a longer period of time than the other isomers. A study of workers in a lindane-producing factory found that levels of β-HCH in blood serum were higher than those of other isomers, and there was a significant correlation between serum levels of β-HCH and length of employment (Baumann et al. 1980). Studies of populations with general HCH exposure have consistently found the level of the β-isomer to be higher than those of the other isomers (Kashyap 1986; Nigam et al. 1986; Ramachandran et al. 1984). This is probably due to the greater tendency of β-HCH to persist and accumulate in the body while the other isomers are more rapidly metabolized or excreted. A survey of epidemiological studies involving workers occupationally exposed to "crude benzene hexachloride" as much as 10–15 years prior to sampling reported serum levels of 20–348 µg/L β-HCH (Morgan and Lin 1978). Unfortunately, none of the above studies specified exposure levels, so it is still questionable whether blood HCH levels can be used as biomarkers to quantify exposure.

There is also a direct correlation between HCH levels in the blood and human adipose tissue and semen (Baumann et al. 1980; Radomski et al. 1971a, 1971b; Szymczynski and Waliszewski 1981); concentrations of β-HCH in subcutaneous adipose tissues were found to be 300 times higher than blood levels (Baumann et al. 1980). Levels of β-HCH detected in skin lipids correlated with those found in human adipose tissue (Sasaki et al. 1991). Although exposure levels for the Japanese people in this study are not known, measuring β-HCH in skin lipids can be a rather easy method of determining relative levels or times of exposure among individuals. β-HCH and γ-HCH have also been found in samples of human maternal

adipose tissue, maternal blood, cord blood, and breast milk in women who were exposed to unknown levels of various organochlorine pesticides in Kenya (Kanja et al. 1992). The metabolites of γ-HCH have been detected in human urine (Angerer et al. 1981). However, such findings are not specific to γ-HCH exposure, and these findings could follow from exposure to both γ-HCH and a number of structurally related compounds.

2.7.2 Biomarkers Used to Characterize Effects Caused by Hexachlorocyclohexane

The individual isomers of HCH can be detected in the blood serum, urine, adipose tissue, and semen of exposed individuals. However, the concentrations measured in these biological tissues have not been exclusively correlated with the degree of adverse health effects observed.

Adverse effects such as neurophysiological and neuropsychological disorders and gastrointestinal disturbances have been reported in workers exposed to HCH during pesticide or fertilizer formulation. Nigam et al. (1986) and Kashyap (1986) reported that nonhandlers indirectly exposed and handlers directly exposed to HCH during pesticide manufacture and formulation were found to have mean serum levels of 0.27 ppm (nonhandlers) and 0.6 ppm (handlers) total HCH. As much as 60–100% of the total HCH measured in serum was β-HCH. The ranges of serum HCH levels measured in all exposed workers were 0.07–0.72 ppm β-HCH, 0.004–0.18 ppm α-HCH, 0–0.17 ppm γ-HCH, and 0–0.16 ppm δ-HCH. Both handlers and nonhandlers complained of paresthesia of the face and extremities, headache, and giddiness; other symptoms included malaise, vomiting, tremors, apprehension, confusion, loss of sleep, impaired memory, and loss of libido. Similar but less-severe effects were noted in 19 maintenance workers who visited the plant frequently. Serum HCH levels measured in these workers were 0.004–0.1 ppm α-HCH, 0.02-0.2 ppm β-HCH, 0–0.32 ppm γ-HCH, and 0–0.04 ppm δ-HCH. Kashyap (1986) also reported higher serum enzyme levels of alkaline phosphatase, lactate dehydrogenase, ornithine carbamyl transferase, γ-glutamyl transpeptidase, and leucine aminopeptidase and increased IgM in the handlers as compared with the nonhandlers and a control population of 14 workers with no occupational contact with HCH. Czegledi-Janko and Avar (1970) reported that γ-HCH blood levels of 0.024–0.16 ppm were associated with clinical symptoms including muscle jerking and variations in EEG in 37 workers exposed to γ-HCH in a fertilizer plant.

HCH and other organochlorine pesticides have been found in the blood serum of some individuals in a population of men attending an infertility clinic in Israel. Serum levels of organochlorine pesticides,

including γ-HCH, have been found in men with low sperm counts to be two times higher than that of fertile men (Pines et al. 1987). Maternal mean serum γ-HCH levels were reported to be higher in cases of premature delivery and spontaneous abortions than in controls (Saxena et al. 1980; Wassermann et al. 1982). Saxena et al. (1980) reported HCH levels of 69.3–550.4 ppb and γ-HCH levels of 30.8–113.6 ppb in the blood of women in India who had experienced spontaneous abortions or premature labor compared with blood HCH levels of 22.2–85.5 ppb and γ-HCH levels of 7.1–32.5 ppb in women who had undergone full-term pregnancy. Serum levels of a number of other pesticides including aldrin, DDE, DDT, and DDD were also found to be higher in cases of premature labor and spontaneous abortions. It was, therefore, not possible to establish a quantitative, causal relationship between the serum HCH levels and these adverse effects.

Blood serum levels of 1–17 ppb β-HCH were not found to be associated with the incidence of colorectal adenocarcinoma in 10 families (Caldwell et al. 1981). Serum levels of 0–49.5 ppb γ-HCH were not found to be associated with the occurrence of hematological syndromes such as pancytopenia, thrombocytopenia, plasma cell myoma, acute leukemia, chronic lymphocytic leukemia, and anemia in 103 patients (Traczyk et al. 1977).

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.8 INTERACTIONS WITH OTHER CHEMICALS

Guinea pigs maintained on diets deficient in vitamin C and protein showed altered γ-HCH metabolism and excretion. Vitamin C deficiency decreased the amount of γ-HCH and its metabolites excreted in the urine and increased the amount stored in the kidney (Chadwick et al. 1972c). Vitamin A supplements decreased HCH-induced toxicity in the rat testes, while deficiencies in vitamin A potentiated the toxicity (Pius et al. 1990).

Cadmium, which is known to inhibit hepatic drug-metabolizing enzymes in mammals, also inhibited the metabolism of γ-HCH in adult male Wistar rats exposed to the compound after short- and long-term pretreatment with cadmium (Chadwick et al. 1978b). Liver microsomal enzymes affected by exposure were γ-HCH dehydrogenase, γ-HCH dechlorinase, and hepatic cytochrome P-450 content. This action altered the profile of metabolites excreted in the urine. Cadmium may inhibit γ-HCH metabolism indirectly by

increasing levels of zinc and reducing levels of copper in the liver (Chadwick et al. 1978b). The addition of cadmium to the diet also increased the concentration of γ-HCH measured in the plasma and liver (Khanna et al. 1988). Cadmium also interacts with γ-HCH to cause significant embryotoxic and teratogenic effects in the developing rat fetus when administered together at a dosage that, for either toxin alone, is insufficient to cause any deleterious effects on development (Saxena et al. 1986).

A low-protein diet potentiated the effects of γ-HCH on reducing the weights of various organs in male rats (Khanna et al. 1990). Serum and liver lipid contents and cholesterol levels were increased in animals fed low-protein diets. The low-protein diet increased the levels of γ-HCH found in the various organ tissues.

The combined application of HCH (mixed isomers) and malathion to the skin of guinea pigs has been shown to produce a more severe toxicity when compared to animals treated with either insecticide alone. The results demonstrate an additive effect between concurrent dermal exposure to malathion and HCH, rather than a synergistic one (Dikshith et al. 1978).

γ-HCH exerts a neurotoxic effect following acute or chronic exposure. γ-HCH is a central nervous system (CNS) stimulant, whereas other isomers of HCH are CNS depressants (McNamara and Krop 1948a). Thus, neurotoxic effects excreted by γ-HCH are inhibited by α-, β-, and δ-HCH (McNamara and Krop 1948a, 1948b; Stein et al. 1980; Van Asperen 1954). "Raw γ-HCH," an intermediate in the production of γ-HCH, contains 16% α-HCH, 7% β-HCH, and 45% γ-HCH (Baumann et al. 1980). This may explain why occupational studies of workers exposed to HCH or γ-HCH manufacturing or application have reported contradictory results with respect to the neurotoxic effects observed.

The metabolism of γ-HCH can be altered by exposure to other chlorinated hydrocarbon insecticides such as DDT. Exposure to various chlorinated hydrocarbon insecticides, including γ-HCH, is thought to produce generalized nonspecific induction of microsomal enzymes. Induction of mixed-function oxidase activity by other chlorinated hydrocarbon insecticides stimulates the selective effect on the oxidative degradation of γ-HCH to the tetrachlorophenols and enhances its elimination in the urine (Chadwick and Freal 1972b). In addition, since HCH is hepatotoxic, therapeutic drops, which produce liver toxicity, such as acetaminophen may also enhance the symptoms of HCH exposure.

Single daily doses of 20 mg/kg γ-HCH in mice significantly reduced the convulsive threshold, as measured by the dose of pentylenetetrazol required to induce seizures 1–4 hours after treatment, but increased the

convulsive threshold 48 hours following treatment (Hulth et al. 1978). A dose of 50 mg/kg γ-HCH significantly increased the convulsive threshold 2, 4, and 10 days following dosing. A single dose of α-HCH significantly increased the convulsive threshold 3 and 24 hours after dosing and resulted in a significant 17% increase in brain levels of γ-aminobutyric acid (GABA) 24 hours after dosing.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to HCH than most persons exposed to the same level of HCH in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or decreased excretion of HCH, or compromised function of target organs affected by HCH. Populations who are at greater risk, due to their unusually high exposure to HCH, are discussed in Section 5.7, Populations With Potentially High Exposure.

People with excoriated (peeling) skin exhibited higher levels in blood of γ-HCH following dermal exposure than those with normal skin (Ginsburg et al. 1977). It was not known if there were any increased toxic effects to individuals with excoriated skin. It is also not known if children are unusually susceptible to the toxic effects of HCH, but anecdotal evidence suggests that it should not be used on infants and young children. The potential hazards of using γ-HCH preparations on infants and young children are underscored by the fact that the very young have a large surface area-to-volume ratio, possibly less efficient hepatic detoxification abilities, and are more likely to lick treated skin (Kramer et al. 1980). Therefore, the use of γ-HCH as a scabicide on infants and very young children, especially those who have very little body fat, has been discouraged (Telch and Jarvis 1982).

Evidence suggests that pregnant women should excercise extreme caution in their exposure to γ-HCH (Ginsburg et al. 1977; Kramer et al. 1980; Solomon et al. 1977a). Refer to Section 2.6 for more detailed explanation. In pregnant animals and humans, γ-HCH crosses the placenta. HCH and γ-HCH body tissue levels have also been associated with premature labor and spontaneous abortions (Rasmussen 1980; Saxena et al. 1980, 1981a, 1981b; Wassermann et al. 1982). However, no causal relationship has been established between blood and tissue levels of γ-HCH and premature termination of pregnancy.

Nair (1996) demonstrated that there is a significant bioconcentration of the α-, β-, and γ-isomers of HCH in the breastmilk of mothers exposed to technical-grade HCH.

People with lowered convulsion thresholds due to epilepsy (treated or untreated), cerebrovascular accidents, or head injuries may be at greater risk of the central nervous system effects of γ-HCH toxicity and may suffer increased risk of or severity of seizures (Kramer et al. 1980; Matsuoka 1981). Those individuals suffering from malnutrition (e.g., low protein, low fiber, and low vitamin intake) may be more susceptible than the general public to the toxic effects of γ-HCH (Rasmussen 1987). Individuals with liver and/or kidney disease may be at risk because of compromised detoxification mechanisms in the liver and impaired excretory mechanisms in the kidney. Additionally, individuals with existing or suspected immunodeficiencies may be at risk because HCH isomers may enhance immunosuppression.

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to hexachlorocyclohexane. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to hexachlorocyclohexane. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following text provides specific information about treatment following exposures to hexachlorocyclohexane: Ellenhorn and Barceloux 1988.

2.10.1 Reducing Peak Absorption Following Exposure

When a large amount of HCH has been swallowed, emetics have been used to induce vomiting. One of the problems with inducing vomiting is that the insecticidal form of HCH is often dissolved in an organic solvent, which presents an aspiration hazard. Activated charcoal can also be used to decrease gastrointestinal absorption. To avoid skin absorption after exposure, clothing should be removed, and the skin should be washed with water and mild soap (Ellenhorn and Barceloux 1988). There are no known methods for reducing absorption following inhalation exposure.

2.10.2 Reducing Body Burden

The traditional methods of increasing elimination or decreasing distribution (e.g., dialysis, diuresis, and hemoperfusion) are not useful because of the high volume of distribution of HCH into adipose tissue (Ellenhorn and Barceloux 1988). HCH accumulates in adipose tissue following all routes of exposure.

However, peritoneal dialysis may be required if rhabdomyolysis (muscle necrosis) leads to myoglobinuria and kidney shutdown (Sunder Ram Rao et al. 1988).

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

Possible mechanisms of action of HCH on some of the target organs have been described. In the nervous system, γ-HCH is thought to interfere with the GABA system by interacting with the GABA-A receptor-ionophore complex at the picrotoxin binding site (Portig and Schnorr 1988; Rivera et al 1991; Sunol et al. 1988). Thus, the seizures caused by γ-HCH can be antagonized by GABA-A mimetics; diazepam is the anticonvulsant of choice (Ellenhorn and Barceloux 1998). Phenobarbital and/or phenytoin or fosphenytoin may be used if seizures are uncontrollable (HSDB 1998). Use of anticonvulsants (especially in children and other susceptible individuals) should include careful monitoring of hypotension, respiratory depression, and the need for endotracheal interbation. In the liver, γ-HCH is thought to produce oxidative stress by inducing oxidative enzymes such as cytochrome P-450 and depleting hepatic glutathione content (Barros et al. 1988, 1991; Srinivasan and Radhakrishnamurty 1988; Videla et al. 1991). Another possible mechanism for hepatic toxicity is increased lipid metabolism (Ravinder et al. 1990; Srinivasan and Radhakrishnamurty 1988). It is possible that interfering with these mechanisms can decrease the toxicity of HCH.

2.11 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of hexachlorocyclohexane is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of hexachlorocyclohexane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

Most of the literature reviewed concerning the health effects of inhaled α-, β-, γ-, or δ-HCH in humans consists of case reports of individuals occupationally exposed or exposed in the home by a γ-HCH vaporizer. The predominant route of exposure in occupational studies is presumed to be inhalation, although dermal exposure is also likely. The health effects in humans associated with ingested HCH are reported primarily in case studies in which individuals ingested pesticide pellets or therapeutic lotions containing γ-HCH to control scabies. Information concerning the health effects of HCH in humans following dermal exposure is limited to case studies of individuals who have misused therapeutic lotions containing γ-HCH to control scabies and head and body lice. The duration and level of exposure to HCH generally cannot be quantified from the information presented in these reports. In addition, the case study reports in humans are limited because concomitant exposure to other toxic substances or other substances present in the atmosphere may have occurred.

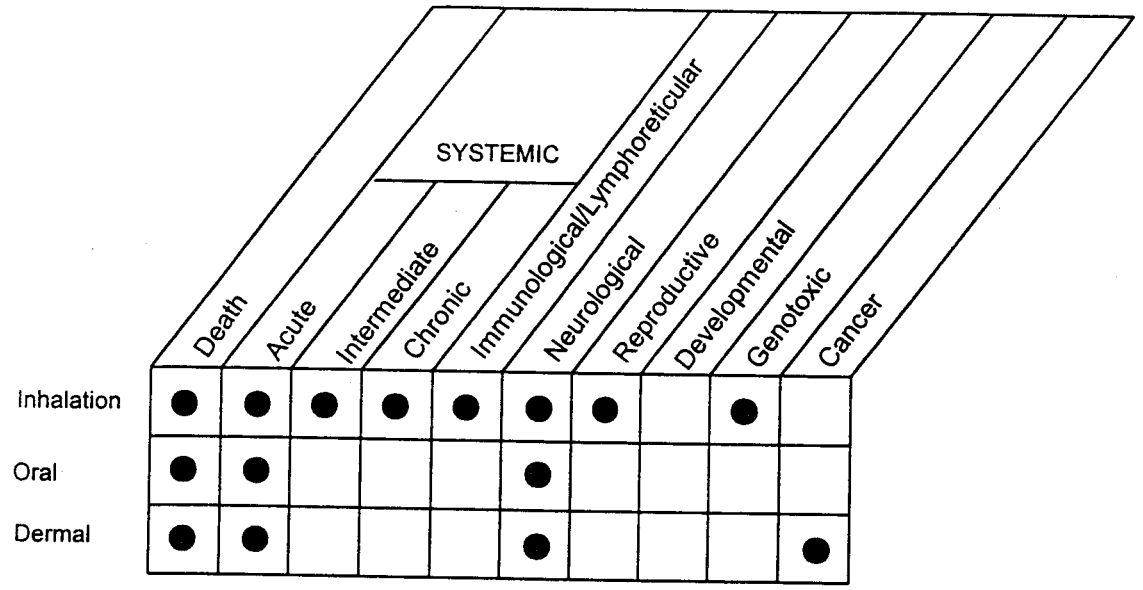
Limited information was found regarding the health effects of lindane following inhalation exposure in animals. The health effects of α-, β-, γ-, and δ-HCH following oral exposure have been well documented in a variety of species. Limited information is available concerning the health effects of technical-grade HCH and lindane following dermal exposure.

γ-HCH is the isomer most thoroughly tested in intermediate- and chronic-duration studies. The carcinogenic effects of technical-grade HCH and α-, β-, and γ-HCH have been examined, but the carcinogenic potential of δ-HCH has not been as well studied. Studies on the long-term effects of dermal exposure to γ-HCH are inadequate for the determination of carcinogenicity status.

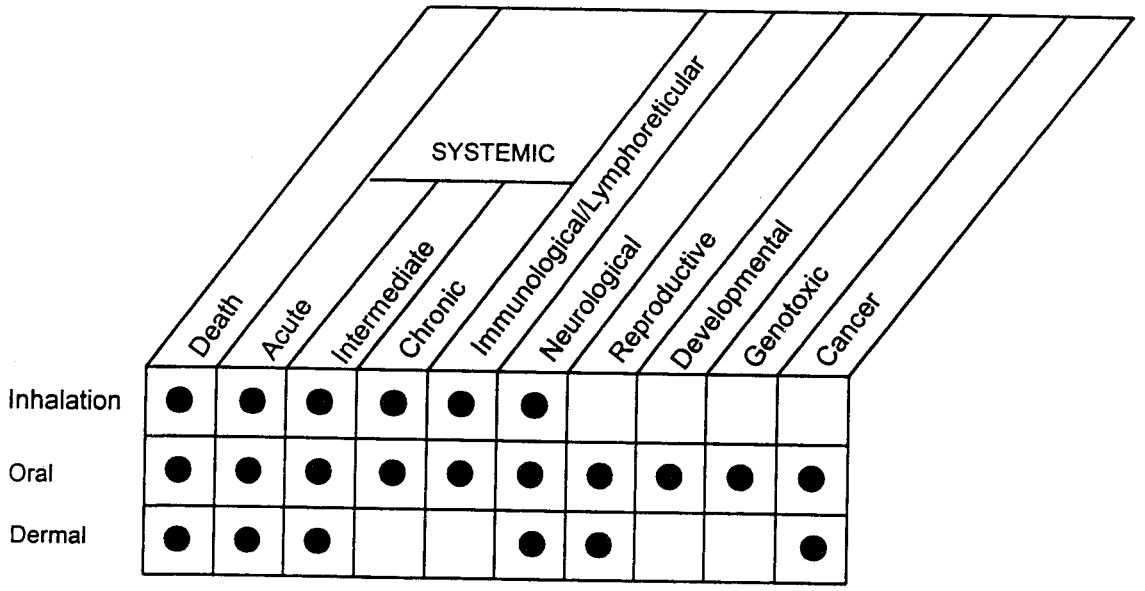
2.11.1 Existing Information on Health Effects of Hexachlorocyclohexane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to HCH are summarized in Figure 2-7. The purpose of this figure is to illustrate the existing information concerning the health effects of HCH. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct

FIGURE 2-7. Existing Information on Health Effects of HCH



Human



Animal

● Existing Studies

comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

2.11.2 Identification of Data Needs

Acute-Duration Exposure. Occasional case reports are available for humans who have had adverse health effects, including irritation of the nose and throat and death, from excessive inhalation exposure from γ-HCH vaporizers (Conley 1952; Loge 1965). Oral exposure to large amounts has resulted in a few human deaths (Storen 1955; Sunder Ram Rao et al. 1988) and adverse neurological, musculoskeletal, and renal effects (Munk and Nantel 1977; Sunder Ram Rao et al. 1988). When applied dermally, γ-HCH has also been shown to have adverse effects such as pulmonary and epicardial petechiae, aplastic anemia, and rashes in a few humans (Davis et al. 1993; Fagan et al. 1981; Rauch et al. 1990). The level of exposure in the human studies generally cannot be quantitated because the information is derived from anecdotal case reports. Therefore, there is little reliable information in humans associating dose with effect. Such information might allow investigators to establish thresholds for systemic toxicity due to acute exposure.

Information on health effects (death and neurological) following acute inhalation of γ-HCH in animals (Ullmann 1986b; Klonne and Kintigh 1988; Oldiges et al. 1980) is limited. Neurological effects following acute inhalation exposure to γ-HCH have included excitation, sedation, ataxia, and spasms (Ullmann 1986b). Acute inhalation studies for the other HCH isomers and technical-grade HCH are not available. No acute inhalation MRL was developed because of insufficient data. Additional acute inhalation data are needed for all isomers, e.g., threshold, dose-response, and target organ. This information is necessary for determining levels of significant human exposure to hexachlorocyclohexane and the associated effects following exposure. An acute oral MRL of 0.01 mg/kg has been developed from data on increased kindling acquisition following exposure to γ-HCH (Joy et al. 1982). An acute oral MRL of 0.2 mg/kg/day for β-HCH has been developed based on ataxia in mice (Cornacoff et al. 1988). Other acute oral studies in animals exposed to γ-HCH have reported death in rats (Gaines 1960) and mice (Liu and Morgan 1986), increased hepatic microsomal mixed-function oxidase activity in mice (Oesch et al. 1982), and degeneration of renal tubular epithelia in rats (Srinivasan et al. 1984). Oral exposure to β-HCH has resulted in an increase in heptatic cytochrome P-450 levels and renal tubular degeneration in rats (Ikegami et al. 1991b; Srinivasan et al. 1984), and exposure to technical-grade HCH has resulted in hepatic focal necrosis, fatty changes, and enzyme activation and renal hemorrhage (Phillip et al. 1989; Ravinder et al. 1989; Dickshith et al. 1990). Additional studies which examine systemic effects (e.g., cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, and

renal) following acute oral exposure to all HCH isomers would be helpful. Acute dermal studies in rats are available on γ-HCH and technical-grade HCH (Dikshith et al. 1991c; Gaines 1960). Acute dermal exposure of rats to γ-HCH (Gaines 1960) or of guinea pigs to technical-grade HCH (Dikshith et al. 1978) was associated with lethality. Additional acute dermal data in animals are needed, for example, threshold, dose-response, and target organs. This information is necessary for determining levels of significant human exposure to HCH and the associated health effects following dermal exposure.

Intermediate-Duration Exposure. Information on human health effects of repeated exposure to HCH is available from studies of occupationally exposed individuals (Kashyap 1986); no information is available on the effects of repeated oral or dermal exposure in humans. EEG abnormalities and increased liver enzymes have been observed in factory workers involved in the production of technical-grade HCH (Kashyap 1986). The exact duration and level of exposure in the human studies are often not provided in the studies. Such information would allow investigators to determine health effects associated with known levels of exposure.

Intermediate-duration inhalation studies of γ-HCH have been performed in rats with mortality reported (Klonne and Kintigh 1988). Inhalation of 603 mg/m^3 γ-HCH for 4 hours or 5 mg/m^3 for 90 days has not resulted in adverse respiratory, hematological, hepatic, or renal effects in rats (Oldiges et al. 1983). However, the data are insufficient for developing an intermediate-inhalation MRL. Additional intermediate-inhalation data in animals are needed, e.g., threshold, dose-response, and target organs. This information is necessary for determining levels of significant human exposure to hch and the associated health effects following inhalation.

Intermediate-duration oral studies have been performed in animals. Oral γ-HCH did not affect the hematological parameter in rats (Suter 1983) and dogs (Rivett et al. 1978). Decrease in blood cell numbers was observed in rats fed β-HCH (Van Velsen et al. 1986) and technical-grade HCH (Joseph et al. 1992c). Hepatic effects in animals following γ-HCH exposure included hypertrophy, necrosis, and cancer (Hanada et al. 1973; Ito et al. 1973; Suter 1983). Hepatic effects in animals, following exposure to β-HCH, included cellular hypertrophy and necrosis (Ito et al. 1973; Van Velsen et al. 1986; Hanada et al. 1973); α-HCH induced hepatic effects included enzyme activation, hypertrophy, necrosis, and cancer (Barros et al. 1991; Hanada et al. 1973; Ito et al 1973). Hepatic effects from technical-grade HCH exposure in animals included changes in enzyme activities and enlargement of hepatocytes, nuclear pyknosis, and vacuolation (Dikshith et al. 1989a, 1991a; Fitzhugh et al. 1950; Karnik et al. 1981; Joseph et al. 1992b). Renal effects from γ-HCH exposure included nephritis, accumulation of protein droplets, hypertrophy, and necrosis (Suter 1983);

nephritis was observed following α-HCH exposure (Fitzhugh et al. 1950). Exposure to β-HCH has resulted in calcinosis and nephritis (Van Velsen et al. 1986; Fitzhugh et al. 1950); technical-grade HCH exposure has resulted in nephritis and tubular necrosis (Dikshith et al. 1991a; Fitzhugh et al. 1950). Two MRLs have been derived for intermediate-duration oral exposure in animals. An intermediate oral MRL of 0.0006 mg/kg/day for β-HCH has been developed based on hepatic effects in rats (Van Velsen et al. 1986). An intermediate oral MRL for γ-HCH of 0.00001 mg/kg/day has also been developed based on immunological effects in mice (Meera 1992).

Intermediate-duration dermal studies have been performed in rabbits, guinea pigs, and rats; some deaths were observed following exposure to γ-HCH (Brown 1988). There are limited data pertaining to systemic effects (e.g., increased respiratory rate and wheezing, hepatic hypertrophy, and basophilic renal tubules) and neurological effects (e.g., hyperactivity, ataxia, and convulsions) in rats following intermediate-duration dermal exposure to γ-HCH (Brown 1988). Death and systemic effects (e.g., hepatic hypertrophy and fatty degeneration and renal tubular necrosis) have been observed in rats (Dikshith et al. 1991c); hepatic hypertrophy and enzyme activation were observed in guinea pigs (Dikshith et al. 1978) following intermediate-duration dermal exposure to technical-grade HCH. Additional intermediate-dermal data in animals are needed, e.g., threshold, dose-response, and target organs. This information is necessary for determining levels of significant human exposure to HCH and the associated health effects following dermal exposure.

Chronic-Duration Exposure and Cancer. Controlled epidemiological studies have been conducted in humans exposed to HCH, but are few in number and limited in scope. Hematological effects have been observed in persons exposed to γ-HCH in the workplace via the inhalation and/or dermal route (Brassow et al. 1981; Jedlicka et al. 1958). A number of case reports are available from individuals who had exposure to γ-HCH in the home, during the handling of the pesticide, or from a nearby formulating plant (Danopoulos et al. 1953; Friberg and Martensson 1953; Gewin 1939; Loge 1965; Mendeloff and Smith 1955). Effects that have been described in these case reports include hematological effects including granulocytopenia, aplastic anemia, paramyeloblastic leukemia, and pancytopenia. Chronic-duration oral studies are not available for humans.

No chronic-duration inhalation studies in animals are available for any isomer. Altered renal excretions and hepatic hypertrophy and have been observed in chronic oral studies on rats with γ-HCH (Amyes et al. 1990). A chronic oral MRL of 0.008 mg/kg/day for α-HCH has been developed based on hepatic effects in rats

(Fitzhugh et al. 1950). Chronic dermal studies in animals are not available. Since there are insufficient data to develop inhalation, and dermal, chronic-duration MRLs, further data from the inhalation and dermal routes are needed (e.g., threshold, dose-response, and target organs). This information is necessary for determining levels of significant human exposure to HCH and the associated health effects. However, the need for dermal studies is not a priority as data on skin absorption can be used to calculate equivalent oral doses.

Use of γ-HCH pesticides by farmers was associated with a 50% increased risk of non-Hodgkin's lymphoma (Blair et al. 1998). However a causal relationship could not be determined due to confounding effects such as use of other pesticides. Limited chronic dermal data in humans are available (Davis et al. 1993), but chronic oral data in humans are not available. There are no inhalation studies in animals. Several chronic toxicity/carcinogenicity bioassays have been conducted in animals following oral exposure to technical-grade HCH and α-, β-, γ-, and δ-HCH (Hanada et al. 1973; Ito et al. 1975; Karnik et al. 1981; Kashyap et al. 1979; Munir et al. 1983; NCI 1977; Thorpe and Walker 1973; Wolff et al. 1987). Chronic dermal exposure to technical-grade HCH caused liver cancer in mice (Kashyap et al. 1979). However, the results were not useful in determining carcinogenic potential because of limitations of these studies, such as testing only one dose and the potential for oral ingestion. 2,4,6-Trichlorophenol, a metabolite of γ-HCH, may be responsible for some or all of the carcinogenic activity observed in mice. This metabolite has been classified by EPA as a group B2 carcinogen. Pentachlorocyclohexene epoxide, a metabolite of γ-HCH that has been identified in the liver of rats, may also be responsible for the carcinogenic effects of γ-HCH. Cancer classifications of several HCH isomers have been made by the U.S. Department of Health and Human Services (DHHS) and the EPA. EPA has classified technical-grade HCH, α-HCH, β-HCH, and δ-HCH as B2, B2, C, and D, carcinogens, respectively (EPA 1998a). γ-HCH has not been assigned a cancer classification by EPA. Additional carcinogenicity information would not be needed at this time. DHHS has classified γ-HCH and other HCH isomers as "reasonably anticipated to be human carcinogen" in the 8th Report on Carcinogens (DHHS 1998). The International Agency for Research on Cancer (IARC) has classified HCH isomers as Group 2B, possibly carcinogenic to humans.

Genotoxicity. HCH did not produce chromosomal aberrations in humans exposed primarily by inhalation (Kiraly et al. 1979). Dominant lethal mutations occurred in mice orally exposed to technical-grade HCH (Lakkad et al. 1982). Increased frequency of polyploid cells occurred in rats exposed orally to α-HCH (Hitachi et al. 1975). Information on the genotoxic effects of γ-HCH is also obtained from *in vitro* studies. Gene mutations were observed in bacteria treated with γ-HCH (with and without metabolic activation) (Moriya et al. 1983; Nagy et al. 1975). γ-HCH was not mutagenic in yeast (Shahin and von Borstel 1977) or

algae (Kar and Singh 1979a). Results of chromosomal aberration tests in γ-HCH-treated hamster cells was questionable (Ishidate and Odashima 1977). Technical-grade HCH produced chromosomal aberrations in cultured human lymphocytes (Rupa et al. 1989d) but did not produce cytogenetic effects in Chinese hamster cells (Murli 1990) or unscheduled DNA synthesis in rat hepatocytes (Cifone 1990). In general, the available information suggests that α-, β-, and γ-HCH may have some genotoxic potential; however, the evidence is not conclusive. Further testing in clastogenicity and genotoxicity tests *in vivo* would be valuable.

Reproductive Toxicity. The only available human data are from one study on hormone levels in pesticide workers in which increases in the levels of serum luteinizing hormone were noted following exposure to γ-HCH for 8 years (Tomczak et al. 1981) . There are no inhalation data in animals for any HCH isomer. Anti-estrogenic properties were found in female rats given γ-HCH by the oral route (Chadwick et al. 1988). Female rabbits treated orally with γ-HCH had a reduced ovulation rate (Lindenau et al. 1994). No adverse effects were reported in a three-generation study in rats treated with 5, 10, or 20 mg/kg/day γ-HCH (Palmer et al. 1978b). Decreased weight gain was observed in the mid- and high-dose group. Oral exposure of rats and mice to β- or technical-grade-HCH has resulted in degeneration of male reproductive organs and sperm abnormalities (Dikshith et al. 1991a; Gautam et al. 1989; Nigam et al. 1979; Pius et al. 1990; Roy Chowdhury and Gautam 1990; Van Velsen et al. 1986), and ovarian atrophy was observed in rats exposed to β-HCH for 13 weeks (Van Velsen et al. 1986). Similar effects were also observed in reproductive organs of rats following dermal treatment with technical-grade HCH for 120 days (Prasad et al. 1995). The reproductive effects on guinea pigs after dermal exposure to technical-grade HCH (100–500 mg/kg/day) have also been investigated (Dikshith et al. 1978). Testicular hypertrophy and atrophy and complete inhibition of spermatogenesis were observed in the guinea pigs. Studies via the inhalation and dermal routes would provide information regarding the reproductive effects of HCH in animals for these exposure routes and could be useful in the assessment of potential reproductive effects in humans.

Developmental Toxicity. Information regarding the developmental effects of HCH in humans was not found for any exposure routes. There are no inhalation data in animals for any isomer. No adverse developmental effects of γ-HCH from oral exposure have been found in rats or rabbits (Khera et al. 1979; Palmer et al. 1978a; Seiler et al. 1994) or from exposure to technical-grade HCH in mice (Dikshith et al. 1990). Alterations in neurotransmitter levels were noted in suckling rats treated once with γ-HCH by gavage (Rivera et al. 1991). No effects on embryonic development were seen in rabbits treated orally with γ-HCH (Seiler et al. 1994). However, decrease in fetal weight, fetal thymic weight, and placental weight have been reported in mice exposed to a single oral dose of γ-HCH on day 12 of gestation (Hassoun and Stohs 1996a). Alterations

in neurotransmitter levels were observed in female rat pups treated orally with technical-grade HCH (Nagaraja and Desiraju 1994). No data on the developmental effects of α-, β-, or δ-HCH were located for the oral or dermal route and there is no information for dermal exposure to technical-grade HCH. Additional developmental studies in animals exposed to α-, β-, or δ-HCH by all three routes would provide information concerning the possible fetotoxic and teratogenic effects in animals, which might be relevant to humans.

Immunotoxicity. A statistically significant increase (approximately 18%) in IgM has been reported in individuals occupationally exposed to technical-grade HCH (Kayshap 1986). The HCH isomer concentrations in serum showed a 10-fold increase when compared to the control. There are no oral or dermal data in humans. Also, there are no inhalation or dermal data in animals. Depressed antibody response to *Salmonella* antigens was reported in rats (Dewan et al. 1980) and rabbits (Desi et al. 1978) exposed to γ-HCH via the oral route. γ-HCH exposure has been shown to result in thymus cortex atrophy, suppressed bone marrow cellularity, erythrocyte precursors, and granulocyte-macrophage progenitor cells in mice (Hong and Boorman 1993). Based on immunological effects of γ-HCH on components of cell- and humoral-mediated immunity in mice, an intermediate oral MRL has been developed (Meera et al. 1992). Decreased lymphoproliferative responses to T-cell mitogens were observed in mice treated by the oral route with β-HCH (Cornacoff et al. 1988). No immunological effects were observed in rats treated with β-HCH by the oral route for 13 weeks (Van Valsen et al. 1986). There is no immunotoxicity data for technical-grade HCH. The biological significance of increased immunoglobulin levels remains to be established. In addition, exposure to technical-grade or γ-HCH may also affect the immune system in humans (Kashyap 1986) and animals (Desi et al. 1978; Dewan et al. 1980). Further studies on all isomers using all three routes of exposure would be useful in the assessment of potential immunotoxic effects in humans.

Neurotoxicity. Exposure to γ-HCH has been shown to be associated with neurological effects in both humans and animals (Czegledi-Janko and Avar 1970; Kashyap 1986; Van Velsen et al. 1986). Paresthesia has been reported in workers exposed via the inhalation or dermal routes (Fonseca et al. 1993; Kashyap 1986). Abnormal EEG patterns have also been noted in workers (Czegledi-Janko and Avar 1970). Seizures and coma have been observed in individuals who have ingested large amounts of γ-HCH (Davies et al. 1983; Harris et al. 1969; Munk and Nantel 1977; Nantel et al. 1977; Powell 1980; Starr and Clifford 1972; Storen 1955). Convulsions have been reported in children following dermal application of γ-HCH (Tenebein 1991; Ramchander et al. 1991). Neurological effects including sedation, restlessness, excitation, and ataxia were seen in rats exposed by inhalation to γ-HCH for 4 hours (Ullmann 1986b). Mice exposed via the inhalation route to γ-HCH in a chronic-study did not display any neurotoxic signs (Klonne and Kintigh 1988).

Convulsions have been observed in rats and mice following oral exposure to γ-HCH (Arisi et al. 1994; Barron et al. 1995; Gilbert 1995; Gilbert and Attia et al. 1991; Joy et al. 1982; Mack 1995; Martinez et al. 1991; Vendrell et al. 1992a; Martinez and Martinez-Conde 1995; Wooley and Griffith 1989). Less serious effects such as decreased myelin and enzyme activity in brain and reduced tail nerve conduction velocity were observed in rats following oral exposure to γ-HCH (Muller et al. 1981; Serrano et al. 1990a). Oral exposure of mice and rats to β-HCH has resulted in lateral recumbency, coma, and reduced tail nerve conduction velocity (Cornacoff et al. 1988; Muller et al. 1981; Van Velsen et al. 1986). Rats and mice exposed orally to technical-grade HCH experienced convulsions, increased motor activity, and variations in neurotransmitter levels (Anand et al. 1991; Dikshith et al. 1991a; Gopal et al. 1992; Kashyap et al. 1979). Neurological effects were not observed in rats following oral exposure to α-HCH (Muller et al. 1981). Information is available on the neurotoxic effects of α-, β-, and γ-HCH in experimental animals following acute-duration oral exposure (Tilson et al. 1987; Tusell et al. 1987; Woolley and Griffith 1989) and intermediate-duration oral exposure (Desi 1974; Muller 1981; Van Velsen 1986). An acute oral MRL of 0.01 mg/kg/day for γ-HCH was derived based on neurological effects (increased kindling acquisition) in rats (Joy et al. 1982). Also, an acute oral MRL of 0.2 mg/kg/day for β-HCH was developed based on ataxia in mice (Cornacoff et al. 1988). Studies in animals have substantiated the neurological symptoms resulting from dermal application of γ-HCH. Effects in rats included sedation, spasms (Ullmann 1986a), tremors, and convulsions (Brown 1988). Neurochemical and neurophysiological studies in animals exposed via the oral route would provide useful information regarding the mechanisms of HCH-related neurotoxic effects. Because an MRL could not be developed for inhalation and dermal exposures, additional studies for all isomers for these two exposure routes would be useful.

Epidemiological and Human Dosimetry Studies. Information on the adverse health effects of HCH in groups of humans comes from reports of occupationally exposed individuals (Brassow et al. 1981; Jedlicka et al. 1958; Kayshap 1986). Adverse health effects include EEG abnormalities, increased liver enzymes, and changes in hematological parameters. Limitations inherent in these studies include unquantified exposure concentrations and durations and concomitant exposure to HCH mixtures and other chemicals and pesticides. The few industrial surveys and studies of exposed individuals generally reported blood levels of HCH following exposure and the health effects associated with these levels (Czegledi-Janko and Avar 1970). However, the reported blood levels of HCH have not been quantitatively correlated with ambient HCH levels or health effects. Studies that provide information correlating exposure levels with body levels of HCH would allow investigators to monitor humans for exposure, including populations living near hazardous waste sites. Well-conducted studies would be helpful in determining and quantifying the effects of inhalation, oral,

or dermal HCH exposure on human health including neurological, hematologic, and hepatic effects. However, considering the magnitude of the needed studies and lowered likelihood of exposure in present day society, the value of such studies is questionable.

Biomarkers of Exposure and Effect

Exposure. Methods exist for the analysis of HCH in blood and urine (Angerer et al. 1981). Thus, biological monitoring for exposure to HCH is possible by measuring the levels of HCH in the blood or urine. In an occupational study, abnormal EEG changes were found to correlate with blood levels of γ-HCH (Czegledi-Janko and Avar 1970). Measurements of γ-HCH represent short-term exposure because it is metabolized and excreted rapidly. Due to its high lipid solubility and persistence, β-HCH level represents long-term exposures. β-HCH has been measured in numerous human tissues and is the isomer that is consistently detected at the highest concentration (Baumann et al. 1980; Kashyap 1986; Morgan and Lin 1978; Nigam et al. 1986; Ramachandran et al. 1984). However, the reported blood levels of HCH have not been quantitatively correlated with ambient HCH levels. Methods that measure the levels of HCH metabolites in urine are not specific enough to detect exposure to HCH alone. More information could be provided by studies designed to correlate biomarkers of exposure with exposure levels.

Effect. No biomarkers of effect, specific for HCH, have been identified in the literature. Nonspecific biomarkers of effect include EEG abnormalities, increases in liver enzymes, hematological effects, seizures and convulsions, neuropsychological, and gastrointestinal effects (Nigam et al. 1986; Kasyup 1986). Muscle spasms and EEG abnormalities have also been observed in workers exposed to γ-HCH (Czegledi-Janko and Avar 1970). High levels of HCH and other organochlorine insecticides have been detected in men with low sperm counts and in women who miscarriage or deliver prematurely (Pines et al. 1987; Saxena et al. 1980; Saxena et al. 1980; Wassermann et al. 1982). No quantitative correlation can be made between body levels of HCH and adverse health effects based on the existing data. Studies quantitatively correlating HCH exposure with body levels of HCH and the occurrence of specific adverse health effects would be useful for monitoring populations possibly exposed near hazardous waste sites. Studies designed to identify specific biomarkers of effect for HCH would be useful.

Absorption, Distribution, Metabolism, and Excretion. Information is available to assess the extent and rate of HCH absorption following oral exposure in animals and humans (Ahdaya et al. 1981; Albro and Thomas 1974; Turner and Shanks 1980). High blood concentrations of γ-HCH have been demonstrated in a number of acute poisoning cases in which humans were exposed to γ-HCH as the result of ingestion (Berry et al. 1987). Animal studies indicate that γ-HCH is readily absorbed from the gastrointestinal tract (Ahdaya et al. 1981). Both *in vivo* and *in vitro* studies that evaluate dermal absorption of γ-HCH in humans are available (Dick et al. 1997a, 1997b). However, absorption of HCH via inhalation can only be inferred from toxicity studies and studies assessing the distribution and excretion of γ-HCH. No quantitative information is available to assess the rate and extent of inhalation absorption in humans or animals. Additional data concerning the absorption of HCH in animals may provide information to assist in characterizing absorption of HCH in humans.

Information on the distribution of HCH isomers in humans is inferred from case studies, clinical studies, and industrial surveys (Baumann et al. 1980; Nigam et al. 1986; Siddiqui et al. 1981a). Air concentrations of α-HCH, β-HCH, and γ-HCH have been found to be associated with blood serum levels in workers (Baumann et al. 1980). HCH isomers have been detected in the adipose tissue of workers (Baumann et al. 1980). γ-HCH was detected in the cerebral spinal fluid of a young boy following ingestion of γ-HCH (Davies et al. 1983). γ-HCH was detected in brain tissue collected during the autopsy of an infant who was treated with a whole-body application of γ-HCH lotion (Davies et al. 1983). The distribution of HCH in animals following oral exposure has been well documented (Chand and Ramachandran 1980; Eichler et al. 1983; Srinivasan and Radhakrishnamurty 1983b). γ-HCH and β-HCH were found to be primarily stored in the fat of rats after acute oral exposure. Except in the brain, β-HCH accumulates in tissues to a greater degree than γ-HCH. α-HCH has been shown to accumulate preferentially in the white matter of the brain (Portig et al. 1989). Data exist on the rate and overall distribution of HCH in animals following dermal application. In guinea pigs, the accumulation of γ-HCH in the brain was greater than in the blood following acute dermal exposure (Solomon et al. 1977a, 1977b).

The metabolism of γ-HCH has been studied in mice and rats (Chadwick and Freal 1972a; Chadwick et al. 1978a; Engst et al. 1979; Kujawa et al. 1977). Researchers have identified the primary metabolites (di-, tri-, and tetrachlorophenols) in humans, rats, and mice. In humans, this information is obtained from urinary excretion studies in which individuals were occupationally exposed to γ-HCH (Angerer et al. 1983; Engst et al. 1979). *In vitro* studies using rat liver microsomes have helped to delineate the major metabolic processes and have demonstrated the formation of a reactive epoxide that may be indicative of similar processes in

other mammals and humans (Fitzloff and Pan 1984). Investigations have not been conducted to examine the epoxide formation *in vivo* or its role in inducing mutagenic and carcinogenic effects. Extensive metabolic studies have been conducted in animals, and adequate studies exist identifying major metabolites in the tissues and urine (Macholz et al. 1982a, 1982b; Chadwick and Freal 1972a; Kujawa et al. 1977). Multiple detoxification pathways have been delineated (Chadwick et al. 1978a, 1981; Kujawa et al. 1977). Further information on the possible role of epoxide formation in carcinogenesis *in vivo*, as well as its rate of formation under various conditions, would be useful.

Information from occupational studies and studies in which γ-HCH was used as a therapeutic lotion is available to conclude that humans excrete HCH, principally as metabolites, in urine, breast milk, and semen (Angerer et al. 1981). Urinary excretion of γ-HCH metabolites by humans has been documented (Angerer et al. 1983). The primary urinary metabolites of γ-HCH are chlorophenols. Quantitative information also exists to conclude that the primary route of HCH excretion in animals, following oral exposure, is urine (Chadwick et al. 1985). There are no inhalation studies that have examined the excretion of HCH. In male rats treated dermally with radiolabeled γ-HCH, radiolabel was detected in the urine (Bosch 1987a).

Comparative Toxicokinetics. Evidence is available to suggest that rats and humans absorb HCH and store the isomers primarily in the fat and other body tissues (Chand and Ramachandran 1980; Eichler et al. 1983; Srinivasan and Radhakrishnamurty 1983b). Similar metabolites have been identified in the urine of exposed individuals and treated rodents, and in both, the primary route of excretion is the urine (Angerer et al. 1981; Chadwick et al. 1985).

Exposure to γ-HCH has been shown to be associated with neurological effects in both humans and animals (Czegledi-Janko and Avar 1970; Kashyap 1986; Van Velsen et al. 1986). The available human and animal data also suggest that HCH isomers may affect the blood system. In addition, HCH isomers may also affect the immune system in humans (Kayshap 1986) and animals (Desi et al. 1978; Dewan et al. 1980). Further studies are not needed at this time.

Methods for Reducing Toxic Effects. Seizures caused by γ-HCH can be antagonized by GABA-A mimetics; diazepam is the anticonvulsant of choice (Ellenhorn and Barceloux 1988). The available data

indicate some ways in which peak absorption of HCH might be reduced following oral or dermal exposure (Ellenhorn and Barceloux 1988). Intestinal absorption can be reduced with activated charcoal, while washing with soap and water can decrease skin absorption. There are no known methods for reducing absorption following inhalation exposure.

Because of the high volume of distribution of HCH into adipose tissue, traditional methods of increasing elimination or decreasing distribution are not useful. Development of methods to enhance the excretion of HCH from adipose tissue, while minimizing toxicity would be beneficial in reducing the body burden.

There is some information on the mechanism (see Section 2.4) for the toxic effects of HCH on the brain (e.g., interference with the GABA system) (Abalis et al. 1985; Casida and Lawrence 1985; Lawrence and Casida 1984) and liver (e.g., disruption of oxidative defense mechanisms) (Barros et al. 1988, 1991; Srinivasan and Radhakrishnamurty 1988; Videla et al. 1991). Further studies in these areas might be helpful for developing methods for reducing toxic effects.

Children's Susceptibility. Limited data are available on the health effects of HCH on exposed children.

It has been demonstrated that weanling rabbits were more sensitive to lindane than young adults, as seen by increased mortality rate and associated excitement and convulsions after treatment (Hanig et al. 1976). However, there is no actual evidence that children are more sensitive to the neurotoxicity of γ-HCH. It would be useful to follow up on the weanling rabbits study and conduct additional studies on immature postnatal animals as an experimental model. Data needs relating to developmental effects are discussed above in developmental toxicity section. Replicating the Dalsenter et al. (1997) study on lactational exposure and adult testosterone levels should be a priority. There is inadequate experimental evidence to determine if pharmacokinetics of HCH in children are different from adults. There is no experimental evidence to indicate whether metabolism of HCH or its mechanism of action is different in children compared with adults. Generally, it would be difficult to have data on the metabolism and mechanism of action of HCH in children (except in accidentally exposed children) to determine whether children are more vulnerable than adults to adverse health effects from exposure to HCH. There are no biomarkers of exposure or effect that have been validated in children or adults exposed as children. There is no data to determine whether there are any interactions with other chemicals that are unique to children or whether interactions observed in adults also occur in children. Although HCH is shown to have some genotoxic potential, it is not known whether parental exposure to HCH may affect children via parental germ cells, or whether HCH may indirectly affect

the fetus during maternal exposure. Additional data is needed to determine the potential for genotoxicity in germ cells and adverse developmental effects.

Child health data needs relating to exposure are discussed in 5.8.1 Data Needs: Exposures of Children.

2.11.3 Ongoing Studies

The following studies involving γ-HCH are ongoing:[a]

INVESTIGATOR	INSTITUTION	SUBJECT	SPONSORED BY
Loch-Caruso, R.	University of Michigan	Lindane modification of uterine muscle	National Institute of Environmental Health
Wooley, D.	University of California, Davis, CA	Physiological effects of acute and chronic exposure to environmental toxicants	U.S.D.A

[a]Information based on data identified in CRIS/USDA (1998) database.

3. CHEMICAL AND PHYSICAL INFORMATION

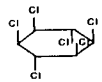
3.1 CHEMICAL IDENTITY

The primary compound, hexachlorocyclohexane, can be further defined by the four major isomers, γ-HCH, α-HCH, β-HCH, and δ-HCH. Lindane refers only to the γ- isomer of HCH and must not contain less than 99.5% of this isomer. The α-, β-, and δ-isomers, as well as technical-grade HCH are not synonymous with lindane (Farm Chemicals Handbook 1993). Technical-grade HCH is not an isomer of HCH, but rather a mixture of several isomers; it consists of approximately 60–70% α-HCH, 5–12% β-HCH, 10–15% γ-HCH, 6–10% δ-HCH, and 3–4% ε-HCH (Kutz et al. 1991). Further information regarding the chemical identity of HCH is located in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of HCH is located in Table 3-2.

TABLE 3-1. Chemical Identity of Hexachlorocyclohexane Isomers[a]

Characteristic	γ-Hexachlorocyclohexane	α-Hexachlorocyclohexane
Synonym(s)	Lindane; 1-alpha, 2-alpha, 3-beta, 4-alpha, 5-alpha, 6-beta-hexachlorocyclohexane; benzene hexachloride-gamma-isomer; BHC; cyclohexane 1,2,3,4,5,6-hexachloro-gamma-isomer; ENT 7796; gamma-benzene hexachloride; gamma-BHC; gamma-hexachlorocyclohexane; gamma-1,2,3,4,5,6-hexachlorocyclohexane; gamma-HCH; gamma-lindane; HCH; HCCH; hexachlorocyclohexane, gamma-isomer; 1,2,3,4,5,6-hexachlorocylohexane, gamma-isomer[a,b]	1-Alpha, 2-alpha, 3-beta, 4-alpha, 5-beta, 6-beta-benzene-trans-hexachloride; alpha-1,2,3,4,5,6-hexachlorocyclohexane; alpha-1,2,3,4,5,6-hexachlorcyclohexane; alpha-benzene hexachloride; alpha-BHC; alpha-HCH; alpha-hexachloran; alpha-hexachlorane; alpha-hexachlorocyclohexane; alpha-lindane; benzenehexachloride-alpha-isomer; cyclohexane 1,2,3,4,5,6-(alpha, DL); cyclohexane 1,2,3,4,5,6-hexachloro-, alpha-; cyclohexane 1,2,3,4,5,6-hexachloro-, alpha-isomer; cyclohexane, alpha-1,2,3,4,5,6-hexachloro-; ENT 9232[a,b]
Registered trade name(s)	Etan 3G (Diachem S.P.A.); Forlin; Gamaphex; Isotox (Chevron Chemical Co.); Germate Plus (Gustafson Inc.); Gamma-Mean 400 and Gamma-Mean L.). (Oregon-California Chemicals, Inc.); Hammer (Exsin Industries); Lindagam; Novigam; Silvanol[c]	No data
Chemical formula	$C_6H_6Cl_6$[a]	$C_6H_6Cl_6$[a]
Chemical structure		
	cis/trans relationship of Cl constituents = 1,2,4,5/3,6[c]	*dis/trans* relationship of Cl constituents = 1,2,4/3,5,6[d]

[a]All information obtained from HSDB 1997 except where noted.
[b]RTECS 1996
[c]Farm Chemicals Handbook 1993
[d]Budavari et al. 1989

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-1. Chemical Identity of Hexachlorocyclohexane Isomers *(continued)*

Characteristic	γ-Hexaxchlorocyclohexane	α-Hexachlorocyclohexane
Identification numbers:		
CAS registry	58-89-9	319-84-6
NIOSH RTECS	GV4900000	GV3500000
EPA hazardous waste	U129; D013	No data
OHM/TADS	7216531	810002
DOT/UN/NA/IMCO shipping	NA 2761 lindane; IMCO 6.1, lindane; UN 2761, organochlorine pesticides, solid, toxic, not otherwise specified	No data
HSDB	646	6029
NCI	C00204	No data

TABLE 3-1. Chemical Identity of Hexachlorocyclohexane Isomers *(continued)*

Characteristic	β-Hexachlorocyclohexane	δ-Hexachlorocyclohexane
Synonym(s)	1-Alpha, 2-beta, 3-alpha, 4-beta, 5-alpha, 6-beta-hexachlorocyclohexane; beta-1,2,3,4,5,6-hexachloro-cyclohexane; beta-benzenehexachloride; beta-BHC; beta-HCH; beta-hexachloran; beta-hexachlorobenzene; beta-lindane; cyclohexane, 1,2,3,4,5,6-hexachloro-, beta-; cyclohexane, 1,2,3,4,5,6-hexachloro-, beta-isomer; cyclohexane, 1,2,3,4,5,6-hexachloro-, trans-; cyclohexane, beta-1,2,3,4,5,6-hexachloro-; ENT 9233; trans-alpha-benzenehexachloride[a,b]	1-Alpha, 2-alpha, 3-alpha, 4-beta, 5-alpha, 6-beta-hexachlorocyclohexane; cyclohexane, 1,2,3,4,5,6-hexachloro-, delta-isomer; cyclohexane, delta-1,2,3,4,5,6-hexachloro-; delta-(AEEEEE)-1,2,3,4,5,6-hexachlorohexane; delta-benzenehexachloride; delta-BHC; delta-HCH; delta-1,2,3,4,5,6-hexachlorocyclohexane; delta-lindane; ENT 9234[a,b]
Registered trade name(s)	No data	No data
Chemical formula	$C_6H_6Cl_6$[a]	$C_6H_6Cl_6$[a]
Chemical structure		
	cis/trans relationship of Cl constituents = 1,3,5/2,4,6[d]	*cis/trans* relationship of Cl constituents = 1,2,3,5/4,6[d]
Identification numbers:		
CAS registry	319-85-7	319-86-8
NIOSH RTECS	GV4375000	GV4550000
EPA hazardous waste	No data	No data
OHM/TADS	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data
HSDB	6183	6184
NCI	No data	No data

TABLE 3-2. Physical and Chemical Properties of Hexachlorocyclohexane Isomers

Property	γ-Hexachlorocyclohexane	α-Hexachlorocyclohexane
Molecular weight	290.83[a]	290.83[a]
Color	White[b]	Brownish to white[c]
Physical state	Crystalline solid[d]; monoclinic prisms[b]	Crystalline solid[c]; monoclinic prisms[a]
Melting point	112.5°C[a,e]	159–160°C[a]
Boiling point	323.4°C at 760 mmHg[c]	288°C at 760 mmHg[c]
Density (g/cm^3)	1.89 at 19°C[f]	1.87 at 20°C[a]
Odor	Slightly musty odor[g]	Phosgene-like odor[c]
Odor threshold:		
Water	12 mg/kg[g]	0.088 ppm for unspecified purity[h]
Air	No data	No data
Solubility:		
Water	17 ppm[i]; insoluble in water[g]	10 ppm[j]; 69.5 mg/L at 28°C[k]
Organic solvent(s)	6.4 g/100 g in ethanol; 20.8 g/100 g in ether; 28.9 g/100 g in benzene[j]	Soluble in alcohol[k]; 1.8 g/100 g in ethanol[l]; 6.2 g/100 g in ether[j]
Partition coefficients:		
Log K_{ow}	3.3[l]; 3.61[m]	3.46[n]; 3.81[m,o]; 3.85[p]
Log K_{oc}	3.0[q]; 3.57[r]	3.57[r]
Vapor pressure	9.4×10^{-6} mmHg at 20°C[e]	0.02 mmHg at 20°C[j]
Henry's law constant (atm m^3 mol^{-1})	7.8×10^{-6}[r]; 3.2×10^{-6}[s]	4.8×10^{-6}[d]; 6.0×10^{-6}[r]
Autoignition temperature	Not flammable[c]	No data
Flashpoint	Approximately 150°F (closed cup)[c]	No data
Flammability limits	Not flammable[c]	No data
Conversion factors	ppm to mg/m^3 in air (20°C): ppm × 4.96 = mg/m^3 mg/m^3 to ppm in air (20°C): mg/m^3 × 0.20 = ppm	ppm to mg/m^3 in air (20°C): ppm × 4.96 = mg/m^3 mg/m^3 to ppm in air (20°C): mg/m^3 × 0.20 = ppm
Explosive limits	No data	No data

[a]Lide 1988
[b]Kirk-Othmer 1985
[c]HSDB 1997
[d]IARC 1979
[e]Budavari et al. 1989
[f]Weiss 1986
[g]Verschueren 1983
[h]Fazzalari 1978
[i]Hollifield 1979
[j]Clayton and Clayton 1981
[k]Kurihara et al. 1973
[l]Geyer et al. 1987
[m]Hansch and Lea 1979
[n]Nakajima 1983
[o]Veith et al. 1979
[p]Pankow et al. 1984
[q]Ripping 1972
[r]Mabey et al. 1982
[s]Mackay and Shiu 1981

TABLE 3-2. Physical and Chemical Properties of Hexachlorocyclohexane Isomers *(continued)*

Property	β-Hexachlorocyclohexane	δ-Hexachlorocyclohexane
Molecular weight	290.83[a]	290.83[a]
Color	No data	No data
Physical state	Crystalline solid[a,d]	Fine plates[a,b]
Melting point	314–315°C[a]	141–142°C[a]
Boiling point	60°C at 0.5 mmHg[a]	60°C at 0.36 mm Hg[a]
Density (g/cm^3)	1.89 at 19°C[a]	No data
Odor	No data	No data
Odor threshold:		
Water	0.00032 mg/kg[g]	No data
Air	No data	No data
Solubility:		
Water	5 ppm[j]	10 ppm[j]
Organic solvent(s)	1.1 g/100 g in ethanol; 1.8 g/100 g in ether; 1.9 g/100 g in benzene[j]	24.4 g/100 g in ethanol; 35.4 g/100 g in ether; 41.4 g/100 g in benzene[j]
Partition coefficients:		
Log K_{ow}	4.50[m]; 3.78[j]; 3.98[l]	2.80[m]; 4.14[n,q]
Log K_{oc}	3.57[q]	3.8[r]
Vapor pressure	0.005 mmHg at 20°C[j]; 2.8×10^{-7} at 20°C[r]	0.02 at 20°C[j]; 1.7×10^{-5} at 20°C[r]
Henry's law constant	4.5×10-7[o,q]	2.1×10-7[p,r]
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors	ppm to mg/m^3 in air (20°C): ppm × 4.96 = mg/m^3 mg/m^3 to ppm in air (20°C): mg/m^3 × 0.20 = ppm	ppm to mg/m^3 in air (20°C): ppm × 4.96 = mg/m^3 mg/m^3 to ppm in air (20°C): mg/m^3 × 0.20 = ppm
Explosive limits	No data	No data

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Table 4-1 lists the facilities in each state that manufacture or process hexachlorocyclohexane, the intended use, and the range of maximum amounts of hexachlorocyclohexane that are stored on site. The data listed in Table 4-1 are derived from the Toxics Release Inventory (TRI94 1996). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

HCH does not occur as a natural substance. The manufacture of technical-grade HCH involves the photochlorination of benzene, which yields an isomeric mixture consisting of α-HCH, β-HCH, γ-HCH, δ-HCH, ε-HCH, and inert *S*-isomers (IARC 1979); this reaction can be started by free-radical initiators such as visual or ultraviolet light, X-rays, or γ-rays (Kirk-Othmer 1985). Treatment with methanol or acetic acid, followed by fractional crystallization, concentrates γ-HCH to the 99.9% required in the technical-grade of γ-HCH (IARC 1979); nitric acid is used to remove odor (SRI 1987). None of the isomers or technical-grade HCH are currently produced in the United States. The production of γ-HCH exceeded 2.27×10^6 g in 1976 (HSDB 1997); commercial γ-HCH production in the United States reportedly ended in that year (EPA 1989b). However, the *Directory of Chemical Producers for 1987 and 1988* lists one producer of γ-HCH, Drexel Chemical Company (SRI 1987, 1988); subsequent volumes (1989–1991) give no listings of γ-HCH producers.

γ-HCH is available in emulsifiable and flowable concentrates, soluble concentrates/liquids, wettable powders, dusts, ready-to-use liquids, pressurized liquids and impregnated materials, oil base and aerosol sprays, granules, and as a smoke generator (Berg 1988; EPA 1985a). γ-HCH is sold separately or in combination with fungicides, fertilizers, other insecticides, or wood preservatives (Hayes 1982).

4.2 IMPORT/EXPORT

γ-HCH is imported to the United States from France, Germany, Spain, Japan, and China (EPA 1985a). The U.S. imports of γ-HCH declined from 1.52×10^8 g in 1977 to 8.53×10^7 g in 1982 (HSDB 1997). No import or export data are available for the other isomers of HCH. Facilities that import HCH for use as a formulation component are shown in Table 4-1. Since HCH is no longer produced in the United States, there is no export of the substance.

Table 4-1. Facilities that Manufacture or Process Hexachlorocyclohexane

State	Location[a]	Range of Maximum Amounts on Site in Pounds[b]	Activities and Uses[c]
Drexel Chemical Co.	Cordele , GA	100,000–999,999	Import , On-site Use/ processing, Formulation Component
Gustafson Inc.	Marsing , ID	100,000–999,999	Formulation Component
Rigo Co.	Buckner , KY	10,000–99,999	Formulation Component
Platte Chemical Co.	Fremont , NE	100,000–999,999	Formulation Component

Source: TRI96 1998

[a]Post Office state abbreviations used

4.3 USE

γ-HCH is used as an insecticide, a therapeutic scabicide, pediculicide, and ectoparasiticide for humans and animals (Budavari et al. 1989). As an insecticide, it is used on fruit and vegetable crops (including greenhouse vegetables and tobacco), for seed treatment, in forestry (including Christmas tree treatment), and for animal treatment. γ-HCH has also been used in vaporizers, but this use was restricted as early as 1951 (Hayes 1982) and banned by the EPA in 1977 (IARC 1979). γ-HCH is registered for use on fruit and vegetable crops, ornamentals, tobacco, greenhouse vegetables and ornamentals, forestry, domestic outdoor and indoor uses by homeowners (including dog dips, house sprays, and shelf paper), commercial food or feed storage areas and containers, farm animal premises, wood or wooden structure sites, and military use on human skin and clothing (EPA 1985b).

Medically, γ-HCH is used topically for the treatment of head and body lice and scabies; it is available in 1% preparations as a lotion, cream, or shampoo (Huff 1988). The γ-HCH used in human and veterinary medicinal and pharmaceutical products must be 99% pure (Budavari et al. 1989). However, the use of γ-HCH for the treatment of scabies can be replaced with Permethrin, a pyrethroid insecticide with lower mammalian toxicity (Franz et al. 1996).

In February 1977, EPA issued a notice of rebuttable presumption against registration and continued registration (RPAR) of pesticide products containing γ-HCH. EPA took this action in response to indications of γ-HCH's potential carcinogenic effect, possible developmental and reproductive effects, possible blood dyscrasias, and delayed toxic effects, as well as its acute toxic effects seen in aquatic wildlife (IARC 1979). In October of 1983, EPA issued a “Notice of Intent to Cancel Pesticide Products Containing γ-HCH.” The contentions concerning developmental and reproductive effects were successfully challenged by industry. EPA no longer permits the use of γ-HCH for purposes involving direct aerial application (EPA 1985b). The notice restricted certain applications of γ-HCH on livestock, structures, and domestic pets to certified applicators or persons under their direct supervision (EPA 1985b). In November 1993, EPA issued a "Notice of Receipt of a Request for Amendments to Delete Uses" for several formulations of lindane powder, 99.5% technical-grade HCH, and dust concentrate, which would delete from the pesticide label most uses of lindane for agricultural crops and use on animals and humans (EPA 1993). Currently, registration for most formulations of lindane have been canceled, with some remaining products registered for restricted use on commercial

ornamentals, avocados, pecans, livestock sprays, forestry, Christmas trees, structural treatments, dog shampoos, and dog dusts (EPA 1998b).

4.4 DISPOSAL

Hexachlorocyclohexane is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1995). Disposal of wastes containing hexachlorocyclohexane is controlled by a number of federal regulations (see Chapter 7).

While current disposal techniques may be adequate, new methods provide increased efficiency and quality of disposal at a greatly reduced cost. The use of demulsification, sorption, and filtration in combination with chemical and biological degradation of pesticide waste waters is being examined. This process is divided into two phases. First, demulsification agents (lignocellulosic materials, peat moss, wood products, etc.) are utilized in the removal of solubilized pesticides. In Phase II, the solid matter (pesticide-saturated sorbents and suspended particulates) are physically separated from the aqueous material through a variety of filtration techniques. The aqueous phase is either recycled or discarded, and the solid phase, in which the concentration of the pesticide is most significant, is further treated through composting (Mullins et al. 1992).

In order to facilitate the composting process, it is important to use sorption agents that provide a beneficial environment for the pesticide-degrading microorganisms. Peat moss, ground pine bark mulch, and steam-exploded wood fibers are excellent demulsifiers because they are highly sorbent, readily available, and inexpensive. They also provide the nutrients required by the degrading microorganisms, although the peat moss media require some carbohydrate enrichment. The solid waste can be either directly metabolized or co-metabolized by multiple species of microbes. The number of compost cycles, and therefore the amount of energy input required, depends on the pesticide concentration and on how easily the pesticide can be biodegraded. In preliminary studies by Mullin et al., this process has reduced the concentration of γ-HCH in waste materials significantly, with less than 1% of the original pesticide remaining after 24-hour incubation (Mullins et al. 1992).

Additional work is required, but the benefits of this disposal technique are clear. It is cost effective, reliable, and it can be adapted to the variety of disposal challenges presented by the multitude of pesticides that are

currently used. The use of microbial consortia ensure that each pesticide will be degraded rapidly. This method can also be used on pesticide mixtures (Mullins et al. 1992).

Disposal methods are currently subject to significant revision by EPA (HSDB 1997).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

α-, β-, γ-, and δ-HCH have been found in at least 112, 128, 163, and 109 of the 1,467 current or former EPA National Priorities List (NPL) hazardous waste sites, respectively (HazDat 1998). The frequency of these sites within the United States can be seen in Figures 5-1, 5-2, 5-3, and 5-4.

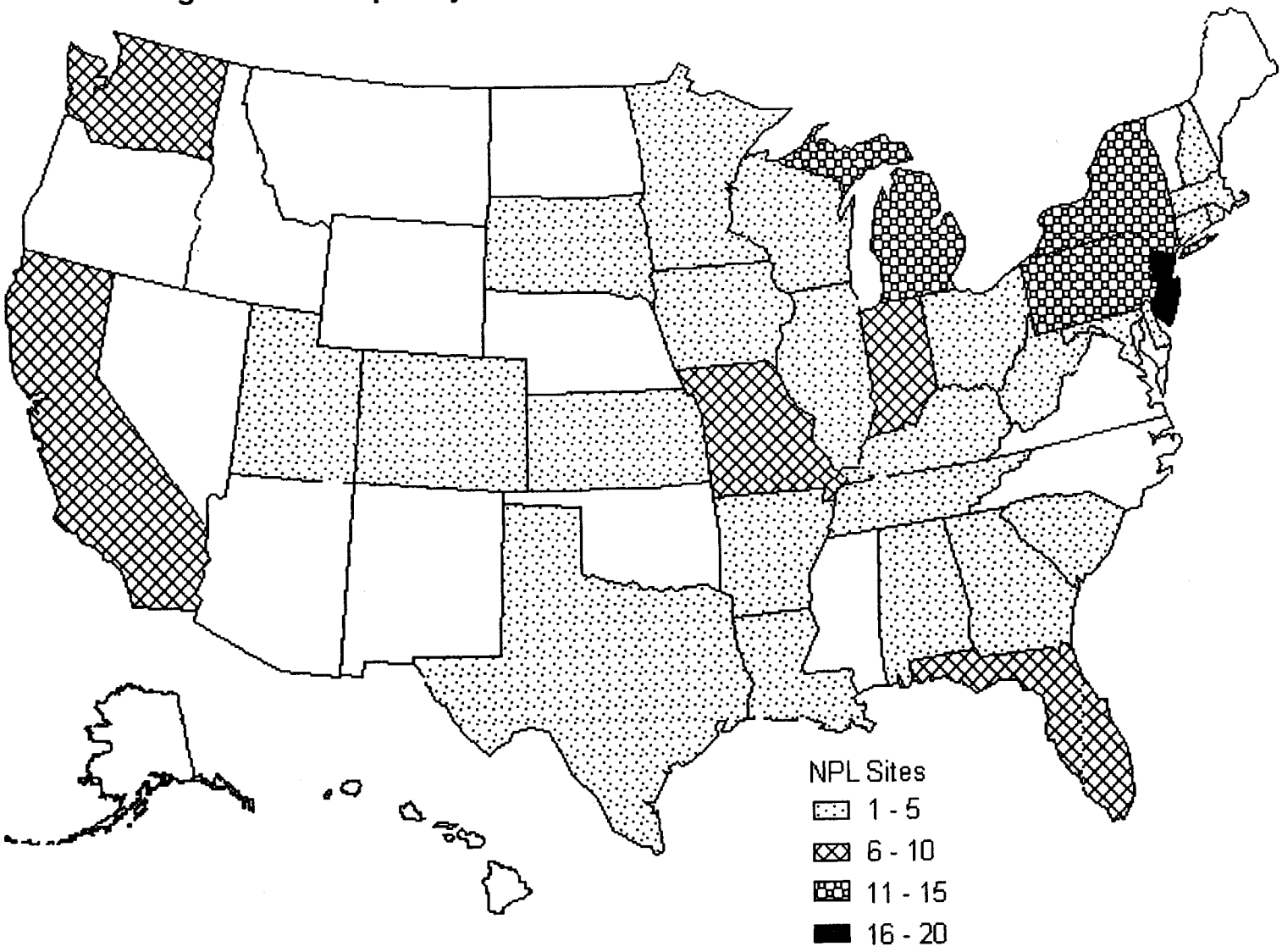
HCH can be released to the environment during the formulation process and through its use as a pesticide. Once released to the environment, HCH can partition to all environmental media. HCH in the atmosphere, either as a vapor or adsorbed to particulates, can be photolytically degraded but is primarily removed from the atmosphere by rain-out and dry deposition. Biodegradation is believed to be the dominant decomposition process for HCH in soil and water. The rates of degradation depend on the ambient environmental conditions. HCH has been detected in air, surface water, groundwater, sediment, soil, fish and other aquatic organisms, wildlife, food, and humans. Human exposure results primarily from medicinal use and from ingestion of contaminated plants, animals, and animal products. HCH has not been found to be a major contaminant of drinking water supplies.

5.2 RELEASES TO THE ENVIRONMENT

According to the Toxic Chemical Release Inventory, in 1996, releases of lindane to the environment from four large processing facilities were 2,429 kg (5,397 pounds) (TRI96 1998). In addition, an estimated 1,664 kg (3,697 pounds) were transferred offsite (TRI96 1998). There were no releases to publicly owned treatment works (TRI96 1998). Table 5-1 lists amounts released from these facilities. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

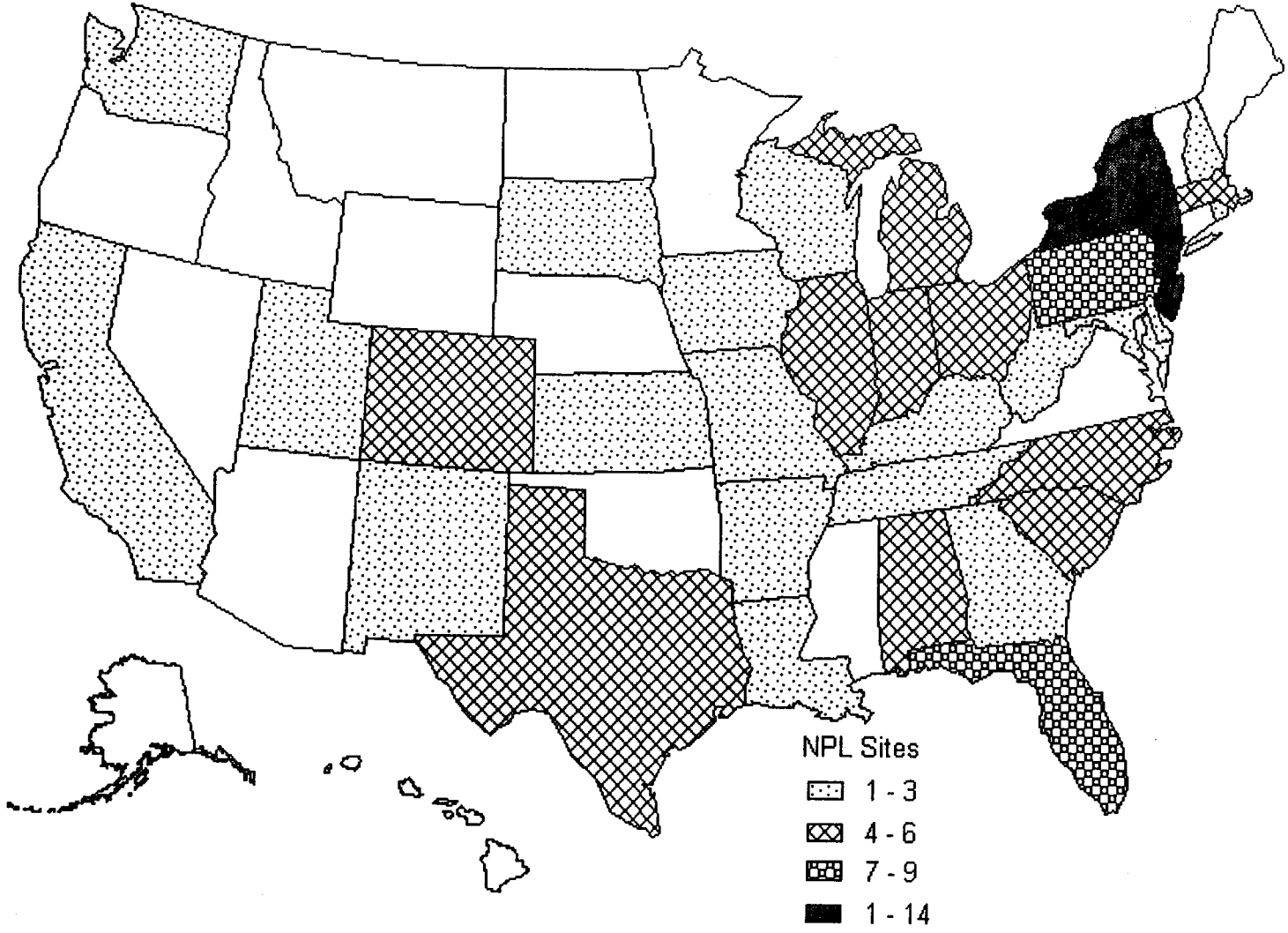
Lindane and other isomers of HCH do not occur naturally in the environment. Most current releases of lindane in the United States are related to its formulation and its use as an insecticide/acaricide.

Figure 5-1. Frequency of NPL Sites with Gamma-HCH Contamination



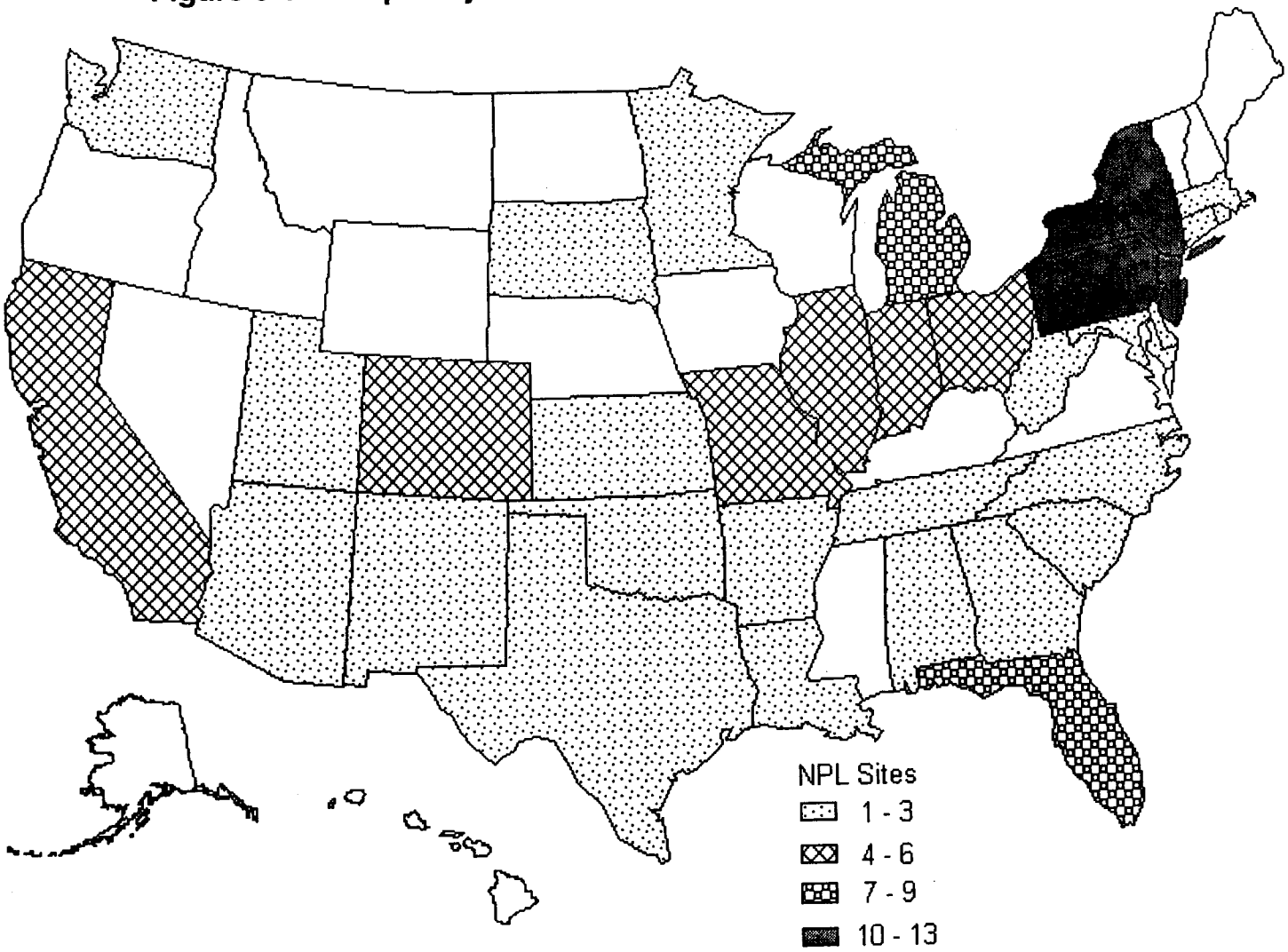
*Derived from HAZDAT 1998

Figure 5-2. Frequency of NPL Sites with Alpha-HCH Contamination



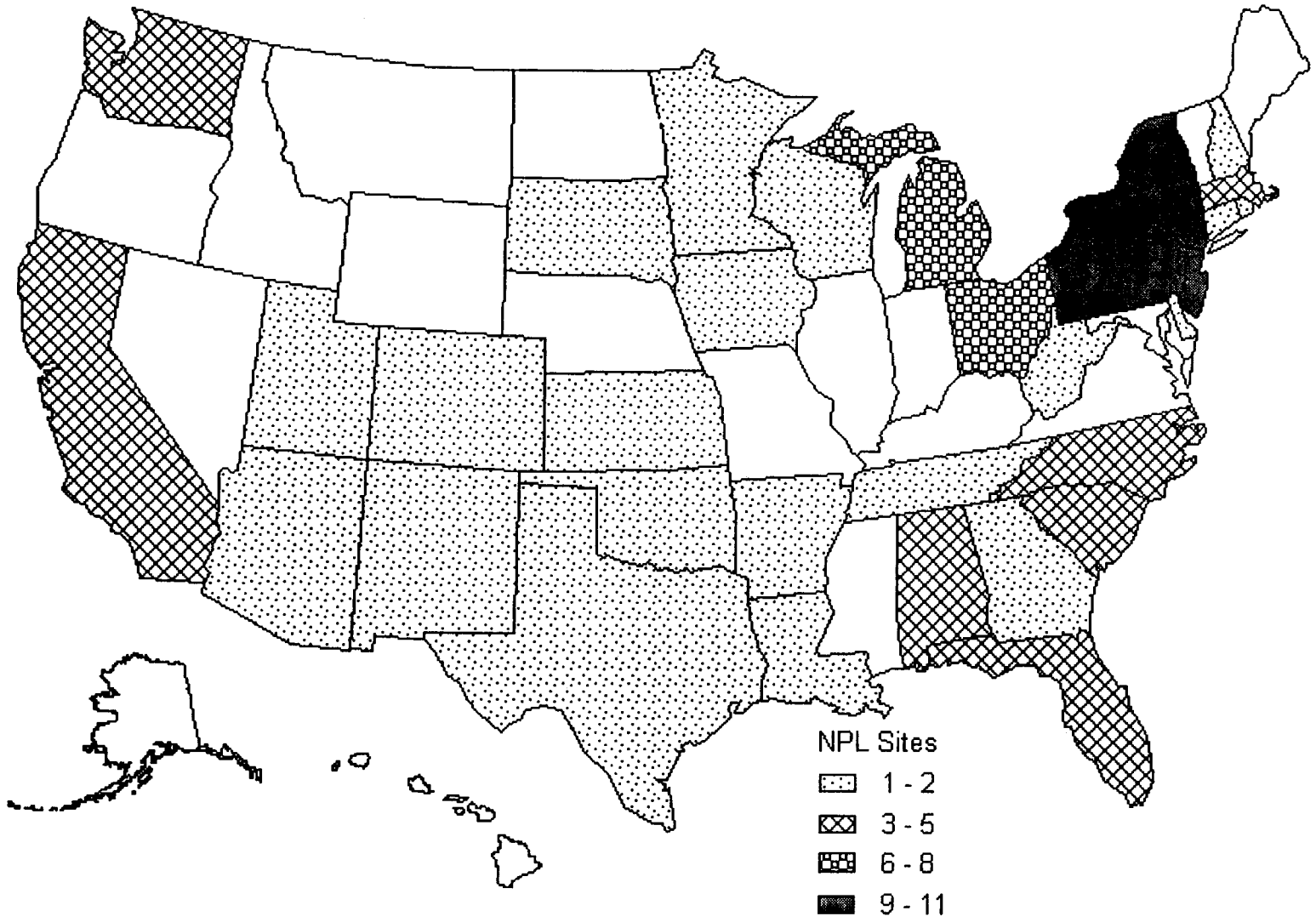
* Derived from HAZDAT 1998

Figure 5-3. Frequency of NPL Sites with Beta-HCH Contamination



*Derived from HAZDAT 1998

Figure 5-4. Frequency of NPL Sites with Delta-HCH Contamination



*Derived from HAZDAT 1998

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Hexachlorocyclohexane

			Total of reported amounts in pounds per year[a]						
State[b]	City	Facility	Air[c]	Water	Land	Underground Injection	POTW Transfer	Off-Site Waste Transfer	Total Environment[d]
GA	Cordele	Drexel Chemical Co.	10	5	250	0	0	0	265
ID	Marsing	Gustafson Inc.	0	0	0	0	0	414	414
KY	Buckner	Rigo Co.	0	0	0	0	0	250	250
NE	Fremont	Platte Chemical Co.	500	0	0	0	0	1,000	1,500
		TOTALS	510	5	250	0	0	1,664	2,429

Source: TRI96 1998

[a]Data in TRI are maximum amounts released by each facility
[b]Post office state abbreviations used
[c]The sum of fugitive and stack releases are included in releases to air by a given facility
[d]The sum of all releases of the chemical to air, land, and water, and underground injection well; and transfers off-site by a given facility

POTW = publicly owned treatment works

5.2.1 Air

According to the Toxic Chemical Release Inventory, in 1996, releases of lindane to the air from four large processing facilities were 510 kg (1,133 pounds) (TRI96 1998). Table 5-1 lists amounts released from these facilities. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Historically, the largest source of γ-HCH releases to the air resulted from agricultural application of the pesticide lindane. Other air releases occurred during the manufacture of the pesticide. Aerial applications of γ-HCH are now prohibited in the United States as its use as a pesticide was restricted (EPA 1985b), and atmospheric releases from these sources are not expected. α-HCH and γ-HCH were detected in 60–90% of the air samples collected in the vicinity of formulation plants in Arkansas and Tennessee in 1971 at mean levels of 1.0 and 1.3 mg/m^3, respectively (Lewis and Lee 1976). Quantitative estimates of the total quantities of γ-HCH released to the air from these sources were not located.

In addition to releases from industrial facilities, γ-HCH is present in the environment as a result of its use or disposal. For example, wind erosion of contaminated soil may distribute pesticides into the atmosphere. γ-HCH can also be released to the atmosphere via volatilization from treated agricultural soils and plant foliage (Lewis and Lee 1976). Evaporative loss of γ-HCH from water is not considered a significant source of atmospheric γ-HCH because of its relatively high water solubility (Mackay and Leinonen 1975). Quantitative estimates of the amount of γ-HCH released from these sources were not located in the literature. Atmospheric release of γ-HCH from disposal sites or hazardous waste sites has not been documented but is likely, considering the physical and chemical properties of γ-HCH.

α, β, γ, and δ-HCH have been detected in air samples collected at 5, 3, 6, and 3 of the 1,467 current or former EPA NPL hazardous waste sites, respectively (HazDat 1998).

5.2.2 Water

According to the Toxic Chemical Release Inventory, in 1996, releases of lindane to the water from four large processing facilities were 5 kg (11 pounds) (TRI96 1998). Table 5-1 lists amounts released from these

facilities. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

γ-HCH can be released to surface water via surface runoff (as the dissolved chemical or adsorbed to particulates) or via wet deposition of rain and snow (Tanabe et al. 1982; Wheatly and Hardman 1965). For example, Lake Ontario received 7 kg/year of α-HCH and <2 kg/year of γ-HCH because of suspended sediment loading from the Niagara River between 1979 and 1981 (Kuntz and Warry 1983). The Great Lakes in general receive from 0.77 to 3.3 metric tons/year of α-HCH and from 3.7 to 15.9 metric tons/year of γ-HCH because of atmospheric deposition of these contaminants (Eisenreich et al. 1981). In 1982, α-HCH and γ-HCH were detected in samples of urban stormwater runoff from Denver, Colorado, and Washington, DC, at 0.0027–0.1 and 0.052–0.1 µg/L in 20% and 11%, respectively, of the 86 samples collected; β-HCH was detected in runoff from Washington, DC, only, in 5% of the samples at a concentration of 0.1 µg/L (Cole et al. 1984).

γ-HCH can be released to groundwater via soil leachate. Although available adsorption data indicate that γ-HCH has a low mobility in soils, the results of monitoring studies suggest that γ-HCH does migrate to groundwater (Page 1981; Sandhu et al. 1978) (see Section 5.4.2). In water tested from 1,076 wells throughout New Jersey, γ-HCH was not detected in at least half of the samples, but a maximum concentration of 0.9 ppb γ-HCH was detected (Page 1981).

α, β, γ, and δ-HCH have been detected in groundwater samples collected at 61, 60, 77, and 58 of the 1,467 current or former EPA NPL sites, respectively (HazDat 1998). α, β, γ, and δ-HCH have been detected in surface water samples collected at 26, 16, 30, and 10 of the 1,467 current or former EPA NPL sites, respectively (HazDat 1998).

5.2.3 Soil

According to the Toxic Chemical Release Inventory, in 1996, releases of lindane to the soil from eight large processing facilities were 250 kg (556 pounds) (TRI96 1998). Table 5-1 lists amounts released from these facilities. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

γ-HCH can be released to the soil by direct application of the pesticide to soil or by direct or indirect releases during formulation, storage, and/or disposal. Hazardous waste sites where γ-HCH has been disposed of in the past are sources of γ-HCH in soils (HAZDAT 1992). However, the application of lindane (purity unspecified) to laboratory refuse columns simulating municipal landfills indicated that lindane did not volatilize or leach from the refuse surface, and movement through the column was slight, suggesting that codisposal of lindane with municipal refuse will result in minimal releases (Reinhart and Pohland 1991; Reinhart et al. 1991).

α, β, γ, and δ-HCH have been detected in sediment samples collected at 13, 16, 30, and 20 of the 1,467 current or former EPA NPL sites, respectively (HazDat 1998). α, β, γ, and δ-HCH have been detected in soil samples collected at 51, 64, 77, and 50 of the 1,467 current or former EPA NPL sites, respectively (HazDat 1998). Also, α, β, γ, and δ-HCH have been detected in leachate collected at 7, 8, 12, and 9 of the 1,467 current or former EPA NPL sites, respectively (HazDat 1998).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

γ-HCH present in soil can leach to groundwater, sorb to soil particulates, or volatilize to the atmosphere. In general, the leaching of organic chemicals through soil is governed by the water solubility of the chemicals and their propensity to bind to soil. Based on the results of a number of laboratory soil column leaching studies that used soils of both high and low organic carbon content as well as municipal refuse, γ-HCH is generally immobile in soils (Hollifield 1979; Melancon et al. 1986; Rao and Davidson 1982; Reinhart et al. 1991). Adsorption of γ-HCH to soil particulates is generally a more important partitioning process than leaching to groundwater. However, groundwater sediments, which have low organic carbon content, are not sufficient to adsorb γ-HCH to the extent that groundwater contamination is prevented (Nordmeyer et al. 1992). In a study involving a laboratory sediment/water system, α- and γ-HCH isomers were highly adsorbed on sediments under both aerobic and anaerobic conditions (Wu et al. 1997).

γ-HCH sorbed to the soil can partition to the atmosphere by wind erosion of surface soil particulates (Stanley et al. 1971) and via volatilization from treated agricultural soils and plant foliage (Lewis and Lee 1976). In tests conducted in a model laboratory system at 10EC and 20EC, volatilization half-lives of γ-HCH from soil and oat plant surfaces of 2.3–24.8 days and 0.29–0.73 days, respectively, were reported (Dorfler et al. 1991a);

half-lives were greater on dry, sandy soils versus peat soils; however, when moisture was added to the soils, the half-life was greater for the peat soil, while the warmer temperature decreased the half-life under all soil and moisture conditions (Dorfler et al. 1991b). In tests performed with a wind tunnel, a volatilization rate of >20% for lindane from soil surfaces within a 24-hour period was determined (Rüdel 1997). The volatilization rate from plant surfaces was 55% for lindane. Application of γ-HCH to fields of sunflowers and sugarbeets resulted in a 54% evaporative loss of the pesticide within 24 hours (Neururer and Womastek 1991).

An analysis of the concentrations of α-HCH to γ-HCH in air over southern Ontario suggested that high levels of γ-HCH were indicative of recent lindane usage (Hoff et al. 1992a). The levels of α-HCH were less variable throughout the year, ranging from 77–260 pg/m^3. During the winter, higher ratios of α-HCH to γ-HCH reflect the movement of air containing the more persistent α-HCH isomer from the colder Arctic regions to the south, while the lower ratios in the summer reflect both increased lindane usage in the region and the lack of movement of Arctic air (Hoff et al. 1992a). γ-HCH is also seen to move with warm air during the summer months from the lower United States (or areas even further to the south) to the Great Lakes region, although a similar trajectory cannot be identified for the more ubiquitous α-HCH. Levels of α-HCH in air are not dominated by volatilization or partitioning to surfaces but are dependent on local temperature changes (Hoff et al. 1992b). α-HCH appears to have a long residence time in the atmosphere and is controlled primarily by transport.

γ-HCH in the atmosphere is likely to be subject to rain-out and dry deposition. γ-HCH removal rates by rainfall and dry deposition were 2.5%/week and 3.3%/week, respectively, and the estimated residence time of γ-HCH in the atmosphere was 17 weeks in a study by Atkins and Eggleton (1971). Rain-out and dry deposition of atmospheric γ-HCH results in the contamination of surface soil and water in areas not directly exposed via pesticide application. γ-HCH concentrations were positively correlated with ambient air temperature although concentrations of α-HCH were not.

In surface waters, γ-HCH has a tendency to dissolve and remain in the water column. Although γ-HCH has a relatively high vapor pressure compared with many other organochlorine insecticides, evaporative loss of γ-HCH from water is not considered to be significant. Mackay and Leinonen (1975) calculated theoretical losses of several pesticides from saturated water solutions and predicted a volatilization half-life of 191 days for γ-HCH.

γ-HCH released to water may undergo adsorption/desorption with sediments and other materials in the water. Adsorption and desorption studies of γ-HCH in natural water-sediment systems performed by Saleh et al. (1982) indicate that a diversity of the natural water-sediment characteristics may affect the sorption-desorption behavior of γ-HCH in addition to the organic carbon content of the sediments. Lindane is sorbed to silt solutions with a slow desorption rate, indicating that transport through the environment is most likely to be particle mediated (Noegrohati and Hammers 1992c). Biosorption of lindane was seen for the fungus *Rhizopus arrhizus* and activated sludge, with equilibrium being reached within 1 and 4 hours, respectively. Death of the sludge biomass resulted in rapid desorption with zero-order kinetics, suggesting that adsorbed lindane can be released back into the environment (Tsezos and Wang 1991a). The sorption of lindane from water using wood charcoal has been described (Keerthinarayana and Bandyopadhyay 1998); it was found to be a good sorbent for the sorption of lindane from water.

Lindane which is adsorbed to sediments may be recycled to the atmosphere as gas bubbles are formed in the sediment by the methanogenesis and denitrification processes of bacteria. It is estimated that in one case studied 85% of the lindane associated with the sediment gas bubbles will be released to the atmosphere, with the remaining 15% being dissolved in the water column as the bubble rises toward the surface (Fendinger et al. 1992).

γ-HCH is bioconcentrated to high levels following uptake from surface waters by a number of aquatic organisms. However, uptake from soils and bioconcentration by plants and terrestrial organisms appears to be limited. For example, bioconcentration factors (BCFs) for γ-HCH from surface waters include 183 in brine shrimp (Matsumura and Benezet 1973), 319 in rainbow trout fry (Ramamoorthy 1985), 84 in pink shrimp, 218 in pinfish, 63 in grass shrimp, and 490 in sheepshead minnows (Schimmel et al. 1977). Introduction of γ-HCH onto sand resulted in a BCF of 95 in brine shrimp and 1,613 in northern brook silverside fish (Matsumura and Benezet 1973). A BCF of 1,273 (lipid basis) in prawns (crustacean) was seen to be 0.58 times the γ-HCH concentration in the underlying sediment, indicating that although aquatic organisms may accumulate γ-HCH from the water column, uptake from contaminated sediment alone may not be extensive (Just et al. 1990). BCFs for the isomers of HCH, using zebra-fish under steady-state conditions, were 1,100 for α-HCH, 1,460 for β-HCH, 850 for γ-HCH, and 1,770 for δ-HCH; BCFs determined by uptake and clearance rate constants were slightly lower (Butte et al. 1991). BCFs on a wet weight basis for γ-HCH in different fish species were positively correlated with their lipid content (Geyer et al. 1997). The bioaccumulation of lindane by tubificide oligochaetes from a static system consisting of sediment and water has been reported (Egeler et al. 1997).

γ-HCH applied to an aquatic mesocosm (i.e., a small, artificial ecosystem) at 61.3 µg/L was reduced by 50% at 24 hours postapplication, while at 19 weeks postapplication the concentration in the water was only 0.2%, and no γ-HCH was detected at 21 weeks. The biological half-life was estimated to be 16.7 days. Movement through the water column was shown by increasing sediment concentrations up to a maximum of 75.4 µg/kg at 96 hours postapplication; however, sediment concentrations decreased to below the detection limit at 23 weeks to give a half-life in sediment of 48.1 days. Rooted aquatic macrophytes have a BCF of 56 at a maximum concentration of 1.7 mg/kg at 24 hours postapplication; however, at 14 weeks all residues were below the detection limit for a half-disappearance time of 18 days. Gastropods in the system had a maximum γ-HCH concentration of 7.2 mg/kg at 24 hours posttreatment, yielding a BCF of 232.4 and a half-disappearance time of 13.7 days with all residues eliminated by 13 weeks (Caquet et al. 1992).

In tests with radiolabeled γ-HCH, grain, maize, and rice plants accumulated 0.95%, 0.11%, and 0.04%, respectively, of the amount of bound residues following 14–20 days growth in a sandy loam soil. Bioconcentration increased by 4–10 times when the plants were grown in test soils containing both bound and extractable residues of γ-HCH (Verma and Pilli 1991). Plants and grains grown on soil treated with γ-HCH showed α-HCH as the predominant isomer although all isomers were found to some extent; amounts decreased with increasing time after application (Singh et al. 1991).

Uptake of γ-HCH by earthworms from a treated humus soil has also been reported. Following exposure to 5 ppm of the compound for up to 8 weeks, the test organisms bioconcentrated γ-HCH by a factor of 2.5. The earthworms biotransformed more than 50% of the accumulated γ-HCH; the main degradation product was γ-2,3,4,5,6-pentachlorocyclohex-1-ene (Viswanathan et al. 1988).

γ-HCH and the other isomers of HCH do not appear to undergo biomagnification in terrestrial food chains to a great extent, although there is a moderate potential for transfer of γ-HCH to animal tissue as a result of soil ingestion or ingestion of contaminated foliage (Wild and Jones 1992). Clark et al. (1974) found that γ-HCH levels in the adipose tissue of cattle were 10 times higher than in the feed (0.002 mg/kg). Szokolay et al. (1977) examined relative accumulation of HCH isomers including γ-HCH and various components in the food chain in Czechoslovakia. Lower γ-HCH residues were found in tissues of animals (chickens, sheep, pigeons) feeding entirely on plant material whereas carnivores had higher concentrations.

The effect of soil loading (the amount of soil deposited per unit area of skin) on the dermal bioavailability of γ-HCH from contaminated soils has been examined (Duff and Kissel 1996). A static *in vitro* diffusion

apparatus and abdominal skin from human cadavers were used. Results indicated that the dermal absorption of γ-HCH from soil is dependent on soil loading and was estimated to be 0.45–2.35%. Dermal absorption of γ-HCH increased significantly with decreases in soil loading providing monolayer or greater coverage of the skin is maintained.

5.3.2 Transformation and Degradation

5.3.2.1 Air

As mentioned earlier, γ-HCH can be present in the air as vapor or sorbed to particulate matter. The widespread global distribution of HCH isomers is indicative of the persistence of γ-HCH in the air. It appears that photodegradation or other degradation processes are not significant in the removal of γ-HCH from air, as compared to rain-out or dry deposition. However, Hamada et al. (1981) found that γ-HCH underwent photodegradation to form two isomers of tetrachlorohexene and pentachlorohexene in propanol solution when irradiated with ultraviolet light produced by a low-pressure mercury lamp. Similar transformation of γ-HCH and other isomers may occur, to some extent, in the atmosphere.

5.3.2.2 Water

Biodegradation is believed to be the dominant degradative process for γ-HCH in aquatic systems, although hydrolysis and photolysis do occur. Sharom et al. (1980) found that <30% of the applied γ-HCH remained in unsterilized natural waters in capped bottles after 16 weeks. Biodegradation was concluded to be responsible for these results, although it was unclear to what extent hydrolysis or adsorption to the glass bottles may have contributed to the results. Zoetemann et al. (1980) estimated river, lake, and groundwater half-lives for γ-HCH from degradation data in these environments to be 3–30 days, 30–300 days, and >300 days, respectively. In natural lake water with a pH of 9.0 and a hardness of greater than 600 mg calcium carbonate/liter, the half-life of γ-HCH was estimated to be 65 hours (Ferrando et al. 1992). Lindane, applied at concentrations of 50 or 500 µg/L to aerobic batch cultures of microorganisms with sodium acetate as a carbon source, was initially removed by adsorption and followed by desorption onto the biomass with subsequent decomposition (McTernan and Pereira 1991). Approximately 56–62% of the lindane was removed from the water column in 23 days, with 26% removal by adsorption onto the biological solids produced in these batch reactors. Microbial growth, using γ-HCH in the absence of sodium acetate, increased as the microorganisms

became acclimated, the pesticide still showed toxic properties, as evidenced by a concurrent increase in microbial death rates.

It has been shown that γ-HCH is degraded by nitrogen-fixing blue-green algae. These algae reduce the toxic effects of γ-HCH following repeated inoculations (Kar and Singh 1979b). The degradation of γ-HCH became more efficient with time, thus reducing the pesticide's toxicity in cultures of nitrogen-fixing blue-green algae. Dechlorination of γ-HCH to γ-pentachlorocyclo-hexene was also shown to occur with fungi in aqueous suspensions (Machholz and Kujawa 1985) and in algal cultures (Sweeney 1969).

Hydrolysis is not considered an important degradation process for γ-HCH in aquatic environments under neutral pH conditions. However, under alkaline conditions, γ-HCH is hydrolyzed fairly rapidly. Saleh et al. (1982) tested rates of hydrolysis of γ-HCH in sterilized natural waters at 25EC and found that hydrolysis of γ-HCH followed first-order kinetics with half-lives of 92 hours at pH 9.3, 648 hours at pH 7.8, and 771 hours at pH 7.3.

Somewhat conflicting information is available on the rate of photolysis of γ-HCH in water. In the study by Saleh et al. (1982) discussed above, the authors also reported γ-HCH first-order photolysis half-lives of 169, 1,791, and 1,540 hours at pH 9.3, 7.3, and 7.8, respectively. The adjusted midwinter half-life of γ-HCH in pure water was reported to be 1,560 hours. However, in another study, γ-HCH rapidly disappeared from a sterile aqueous solution when exposed to ultraviolet radiation in atmospheric nitrogen; less than 1% of the original amount was left in solution after 30 hours of exposure (Malaiyandi et al. 1982). Photolysis of lindane in aqueous solution in the presence of polyoxomethallate and ultraviolet light has been demonstrated (Hiskia et al. 1997).

5.3.2.3 Sediment and Soil

γ-HCH in soil or sediment is degraded primarily by biotransformation; however, the major removal mechanism for γ-HCH from soils, at least in warm climates, is the volatilization of the compound from soil surfaces. A 6-fold increase in γ-HCH volatilization from soil was seen when the temperature increased from 15EC to 45EC; flooding the soil also increased the volatilization (Samuel and Pillai 1990). Tu (1976) reported that 71 of 147 microorganisms isolated from a loamy sand soil were able to utilize a γ-HCH solution as the sole carbon source. White rot fungus degraded radiolabeled γ-HCH in aerobic pure culture laboratory tests. In a silt loam soil/corncob test matrix, 34.7% of the compound was degraded over a 60-day

test period, whereas 53.5% degradation was observed in liquid cultures over a 30-day test period (Kennedy et al. 1990). The results of this study have been confirmed by more recent studies (Mougin et al. 1996; Mougin et al. 1997). The isolation of γ-HCH-degrading bacteria, classified as *Sphingomonas paucimobilis*, from contaminated soils has been reported (Thomas et al.1996). A *Pseudomonas* species has also been isolated from pretreated soil that is able to degrade γ-HCH and α-HCH, but not β-HCH, within 10–20 days under both flooded (anaerobic) and unflooded (aerobic) conditions; greater degradation rates were observed under aerobic conditions (Sahu et al. 1993). However, the concentrations and persistence of γ-HCH in soil are dependent on soil types. An analysis of two soil types, loamy sand (approximately 1–2% organic matter) and muck (approximately 27–56% organic matter), for γ-HCH residues showed that mean residues in the loamy sand soil had decreased from 95 ppb dry weight in 1971 to below the detection limit of 10 ppb in 1989; however, in muck, residues had decreased from 426 ppb in 1971 to 168 ppb in 1989 (Szeto and Price 1991). The presence of crops on the soils also affects the persistence of HCH residues, with half-lives of 58.8 days and 83.8 days for cropped and uncropped plots, respectively. β-HCH was the most persistent isomer with half-lives of 184 and 100 days, respectively, on cropped and uncropped plots; γ-HCH was next at 107 and 62.1 days, followed by α-HCH at 54.4 days and 56.1 days, and finally, δ-HCH at 33.9 and 23.4 days. Only trace amounts of the isomers were found to leach below 20 cm soil depth (Singh et al. 1991). The β-HCH isomer comprised 80–100% of the total HCH residues found in soil or vegetation on land surrounding an industrial landfill in Germany 10 years after the final HCH input (Heinisch et al. 1993).

Most available information suggests that γ-HCH transformation is favored in biologically rich, anaerobic environments (Callahan et al. 1979; Haider 1979; Kalsch et al. 1998). In bench-scale anaerobic digestion tests designed to assess the fate of semivolatile organic pollutants in primary and secondary sludges, γ-HCH was found to undergo 98% degradation at 120 days. Sorption of the compound to the digester solids accounted for 2% of the initial feed; none of the compound was lost by volatilization. The digesters were operated at 35EC with a 30-day solids retention time (Govind et al. 1991). Similar results were seen with live activated sludge where initially reversible biosorption dominates the removal process followed by an increased aerobic biodegradation after approximately 10 hours of acclimation. The biodegradation process includes hydrolytic dechlorination with subsequent ring cleavage and finally, partial or total mineralization (Tsezos and Wang 1991b). Adaptation of sewage sludge is slow and may take 1–2 months; however, once acclimation occurs, 70–80% biodegradation of γ-HCH may occur, with the percentage of degradation decreasing with increasing sludge age (Nyholm et al. 1992). Co-oxidation or reductive dechlorination are the probable degradation mechanisms (Jacobsen et al. 1991; Nyholm et al. 1992).

Numerous diverse studies on biological degradation have shown that γ-HCH was transformed to tetrachlorohexene; tri-, tetra-, and pentachlorinated benzenes; penta- and tetra cyclohexanes; other isomers of HCH; and other related chemicals. The products varied depending on what organisms were present, what products were sought, and when the sample was analyzed (Callahan et al. 1979). Laboratory studies have demonstrated the bioisomerization of γ-HCH to α-, β-, and δ-HCH but bioisomerization in the environment was considered to be nonsignificant by an investigator who conducted a field study (Waliszewski 1993). Levels of individual isomers were approximately 0.1–1.4% and 0.8–4.0% of the γ-HCH concentrations at 3–31 weeks and 34–46 weeks, respectively, following γ-HCH treatment of soil. An inability to control all environmental conditions in the laboratory was discussed as a possible reason for differences in results between laboratory and field studies.

Abiotic transformation and degradation processes of γ-HCH in soil/sediment are not thought to be significant pathways. As discussed earlier for water, photolysis or hydrolysis are not considered important degradation pathways of γ-HCH and other isomers.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to hexachlorocyclohexane depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on hexachlorocyclohexane levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

5.4.1 Air

γ-HCH was detected in ground level ambient air samples collected in College Station, Texas, in 1979–1980 at a mean concentration of 0.23 ng/m^3 (range, 0.01–1.60 ng/m^3) (Atlas and Giam 1988). The compound has also been detected in troposphere air samples collected over the Adirondack Mountains in New York state in 1985 at a mean concentration of 0.509 ng/m^3 and over Newport News, Virginia, in 1988 at a mean concentration of 0.021 ng/m^3 (Knap and Binkley 1991). Air monitoring over southern Ontario, Canada, from July 1988 to July 1989 showed annual mean air concentrations of α-, β-, and γ-isomers to be 0.145, 0.0018, and 0.06 ng/m^3 with a total HCH annual mean concentration of 0.21 ng/m^3 and with the greatest total HCH concentrations during the summer months (Hoff et al. 1992a).

In a study of global distribution and atmospheric transport of chlorinated hydrocarbons in the West Pacific, Eastern Indian, and Antarctic Oceans, Tanabe et al. (1982) confirmed the widespread distribution of HCH isomers. HCH residues were detected in all 79 air and water samples collected. The concentrations ranged from 1.1 to 2.0 ng/m^3 in air and from 3.1 to 7.3 ng/L in water. Other monitoring studies include the detection of γ-HCH in the lower troposphere over the Southern Indian Ocean in 1986 at a mean concentration of 0.406 ng/m^3 (Wittinger and Ballschmiter 1990), in the lower troposphere over Bermuda in 1988 at a mean concentration of 0.012 ng/m^3 (Knap and Binkley 1991), and in ambient air samples collected at Axel Hieberg Island in the Canadian arctic at 0.017–0.07 ng/m^3 (Hargrave et al. 1988).

γ-HCH has also been detected in rainfall samples collected in College Station, Texas, in 1979–1980 at a weighted mean concentration of 2.81 ng/L (range, 0.30–7.8 ng/L) (Atlas and Giam 1988) and in Bermuda in 1983–1984 at a mean concentration of 0.126 ng/L (range, 0.001–0.936 ng/L) (Knap et al. 1988). In rainfall samples collected at four sites in Canada in 1984, γ-HCH concentrations ranged from 0.46 to 34 ng/L (Strachan 1988). The mean concentration in rainfall samples collected at Lake Superior during the 1984 wetfall season was 3.0 ng/L, with an annual loading of 2.0 μg/m^2/year (Strachan 1988). These values were less than those determined in the years 1977, 1981, and 1983 (Strachan 1988). γ-HCH has been detected in rain and snow water in Portland, Oregon in 1982 at mean concentrations ranging from 0.45 to 11 ng/L (Pankow et al. 1984). Rainwater collected in Hawaii in 1970–1971 had a mean γ-HCH concentration of 5 ng/L, with concentrations ranging from 1 to 19 ng/L (Bevenue et al. 1972). Snow and ice samples collected at Axel Hiberg Island in the Canadian Arctic in 1986 contained γ-HCH at concentrations of 0.211–0.644 ng/L and 0.186 ng/L, respectively (Hargrave et al. 1988). Rain samples collected in Germany between June 1990 and August 1991 contained γ-HCH at a mean concentration of 0.208 μg/L (range, 0.020–0.833 μg/L; detection limit, 0.5 pg) in 39 of 41 samples (Scharf et al. 1992).

5.4.2 Water

Surface water concentrations of γ-HCH have been measured in many areas across the United States. Reported concentrations ranged from 10 to 319 parts per ton (ppt) (mean concentration of 147 ppt) in Hampton County, South Carolina (Sandhu et al. 1978), to much higher concentrations of 0.052–0.1 parts per billion (ppb) in Washington, DC, and Denver (Cole et al. 1984). The majority of the available monitoring studies were conducted in the early to mid 1970s. The most recent monitoring study was conducted in 1980–1981 in the Niagara River near its entry into Lake Ontario. In that study, γ-HCH was detected in 99% of all samples at a mean concentration of 2.1 ppt (Kuntz and Warry 1983). γ-HCH concentration in Lake

Michigan tributary streams ranged from undetected to 0.15 ppb (Schacht et al. 1974). According to EPA's STORET database, γ-HCH was detected in 27% of 4,505 surface water samples collected in the United States at a median concentration of 0.020 µg/L (Staples et al. 1985). γ-HCH concentrations in groundwater samples were greatest in the West South Central region (Phillips and Birchard 1991). The compound was also found in water samples collected in Lake Ontario in 1983 at 0.806–1.85 ng/L concentration (Biberhofer and Stevens 1987).

γ-HCH has been detected in more than 10% of urban stormwater runoff samples in two U.S. cities at concentrations between 0.052 and 0.1 ppt (Cole et al. 1984). In urban runoff samples collected in the Canadian Great Lakes Basin, γ-HCH was detected at mean concentrations of 0.0065 µg/L and 0.0035 mg/kg in the aqueous and sediment portions, respectively; the mean annual loading of the compound in runoff in the basin was reported to be 4.1 kg/year (Marsalek and Schroeter 1988).

γ-HCH has been detected in groundwater at a median concentration of 16 ppt in Chesterfield County, South Carolina, and 163 ppt in Hampton, South Carolina (Sandhu et al. 1978). A concentration range of undetected to 0.9 ppt was reported for groundwater samples from New Jersey. γ-HCH has also been detected in drinking water from Cincinnati, Ohio (Keith et al. 1976); Hampton, South Carolina (Sandhu et al. 1978); and Oahu, Hawaii (Bevenue et al. 1972), at mean concentrations of 0.01 ppt, 10 ppt, and 0.2 ppt, respectively. In a study of α-HCH and γ-HCH in Saskatchewan, Canada, these HCH isomers were not detected frequently in surface waters that originate from ground water (Donald et al. 1997).

5.4.3 Sediment and Soil

According to EPA's STORET database, γ-HCH was detected in 0.5% of 596 sediment samples collected throughout the United States at a median concentration of <2.0 µg/kg (Staples et al. 1985). According to data collected in STORET between 1978 and 1987, γ-HCH was found in the greatest concentration in sediment from the West North Central census region of the United States, followed by the Mountain region and the East South Central region (Phillips and Birchard 1991). γ-HCH was detected in 33% of suspended sediment samples collected from the Niagara River; the average concentration was 2 ppb (Kuntz and Warry 1983). The average γ-HCH concentration in settling particulates from Lake Ontario was 2.4 ppb in 1982 (Oliver and Charlton 1984). Sediment samples from Lake St. Francis on the St. Lawrence River contained a mean total HCH concentration of 0.6 ng/g dry weight (range, <0.1–2.0 ng/g), suggesting that deposition of contaminated materials from Lake Ontario was of less importance than local inputs of HCH (Sloterdijk

1991). γ-HCH concentrations in creek sediments collected in 1976 near the James River in Virginia ranged from 7.3 to 8.5 ppb (Saleh et al. 1978). γ-HCH was included in the analytes monitored in the National Oceanic and Atmospheric Administration's (NOAA) Status and Trends Mussel Watch Program conducted in the Gulf of Mexico. The compound was detected in 19% of the sediment samples collected in 1987 at a mean concentration of 0.07 ng/g (median, <0.02 ng/g; range, <0.02–1.74 ng/g) (Sericano et al 1990). Sediment samples collected around the Great Lakes in May 1989, contained γ-HCH concentrations ranging from below the detection limit (0.10 µg/kg) to 0.99 µg/kg (wet weight) (Verbrugge et al. 1991). Thirty-three sediment samples from 11 impoundments along the Indian River Lagoon in Florida contained γ-HCH at concentrations ranging from 34.4 ng/g in the top layer of sediment at one impoundment to 9.4 ng/g in the bottom layer at the same site (Wang et al. 1992). The pesticide lindane had been used for mosquito control in the area from the late 1950s to the mid 1960s. Interstitial water samples from the impoundment sites did not contain detectable levels of the pesticide.

5.4.4 Other Environmental Media

γ-HCH residues were detected in fat samples of domestic farm animals collected in Ontario, Canada, in 1986–1988. Mean concentrations in fat from chickens, turkeys, beef, lamb, and pork ranged from 0.012 to 0.032 mg/kg; the mean concentration in hen eggs was 0.008 mg/kg (Frank et al. 1990b).

Residues of γ-HCH on tomatoes decreased by 23.9%, 15 days after application of the pesticide (from 195.6 µg/kg to 148.8 µg/kg). Processing the tomatoes (e.g., pureeing, making tomato juice) reduced the residue levels by 100% after the waiting period; however, washing the tomatoes reduced the residues by up to 55.9% (Bessar et al. 1991). A pesticide residue screening program carried out by the H.E.B. Food Stores of San Antonio between 1989 and 1991 detected γ-HCH in 4 of 429 onion samples (detection limit, 0.02 ppm); however, none of the positive samples exceeded the action level for this commodity (Schattenberg and Hsu 1992).

As part of NOAA's Status and Trends Mussel Watch Program conducted in the Gulf of Mexico, γ-HCH was detected in 80% of the oyster samples collected in 1987 at a mean concentration of 1.74 ng/g (median, 1.20 ng/g; range, <0.25–9.06 ng/g) (Sericano et al. 1990). Samples taken in 1992 from Mexico's Palizada River, located in a major agricultural area with substantial pesticide use, contained an average γ-HCH concentration of 0.08 ng/g in shrimp but no detectable levels in oysters or mussels (Gold-Bouchot et al. 1995). Combined concentrations of other HCH isomers were found to be 1.18 ng/g in shrimp, 1.04–1.97 ng/g in oysters, and

1.68 ng/g in mussels. Schmitt et al. (1985) reported the results of a monitoring study of fish tissues from 107 freshwater stations in the United States. A decline in tissue occurrence of detectable α- and γ-HCH residues was observed from 1976 to 1981. During 1980–1981, whole body residues of γ-HCH exceeded 0.01 ppb at only one station, where levels were 0.02–0.03 ppb. Tissue concentrations of α-HCH were higher than γ-HCH. The highest concentrations for α-HCH were 0.03–0.04 ppb and were found in fish from the southwestern and midwestern United States. An analysis of fish from the Upper Steele Bayou in Mississippi in 1988 indicated that β-HCH concentrations ranged from undetected to 0.02 mg/kg wet weight in fish; no β-HCH was detected in snakes or sediments taken from the same area (Ford and Hill 1991). Atlantic cod taken from relatively isolated stock in the southern Gulf of St. Lawrence showed declining tissue concentrations of α-HCH between 1977 (1.865 µg/kg) and 1985 (1.792 µg/kg).

An analysis of pesticide residues in green coffee and after roasting indicated that technical-grade HCH was found in green coffee at concentrations ranging from <0.005 ppm to 0.204 ppm. However, storage and roasting reduced the pesticide residues by 60–67% and up to 98%, respectively, with darker roasting resulting in the greatest reduction (McCarthy et al. 1992).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Human exposures to γ-HCH can result from the ingestion of plants, animals, animal products, milk, and water containing the pesticide. Farm animals may be exposed to the compound through feed, air, or water or cutaneous application for protection from ectoparasites. Lipophilic pesticides such as γ-HCH accumulate in adipose tissue. Clark et al. (1974) found that γ-HCH levels in the adipose tissue of cattle were 10 times higher than in the feed (0.002 mg/kg). An analysis of data from 238 families in Missouri between June 1989 and March 1990, indicated that 9.2% of the families reported using Kwell shampoo (contains γ-HCH) for lice control on children (Davis et al. 1992).

The most likely route of nonmedicinal human exposure to γ-HCH is ingestion of food containing the pesticide. A smaller degree of exposure may result from ingestion of drinking water containing γ-HCH. For example, γ-HCH was detected in 6% of the foods collected in eight market basket surveys from different regions of the United States during the period of April 1982 to April 1984 (Gunderson 1988). Foods representative of eight infant and adult population groups were prepared for consumption prior to analysis in a revision to FDA's Total Diet Studies methodology. The estimated mean daily intakes (ng/kg body weight/day) of γ-HCH for these groups in 1982–1984 were as follows: (1) 6–11-month-old infants, 1.9;

(2) 2-year-old toddlers, 7.9; (3) 14–16-year-old females, 3.1; (4) 14–16-year-old males, 3.4; (5) 25–30-year-old females, 2.0; (6) 25–30-year-old males, 2.5; (7) 60–65-year-old females, 1.6; and (8) 60–65-year-old males, 1.8. γ-HCH intakes (ng/kg body weight/day) for three of these groups in 1988 were estimated in the FDA's Total Diet Analyses to be as follows: (1) 6–11-month-old infants, 0.8; (2) 14–16-year-old males, 1.4; and (3) 60–65-year-old females, 0.9 (FDA 1989b). HCH isomers have been detected in the following feed types formulated for infants and toddlers: whole milk and other dairy products; meat, fish, and poultry; oils and fats; vegetables; and sugars and adjuncts (Gartrell et al. 1986a).

HCH isomers were also detected in adult diet foodstuffs, including dairy products; meat, fish, and poultry; garden fruits; oils and fats; leafy and root vegetables; and sugar and adjuncts (Gartrell et al. 1986b). Daily intake values of HCH isomers in adult diets in 1981–1982 were reported to be 0.010 μg/kg/day for total HCH; 0.008 μg/kg/day for α-HCH; <0.001 μg/kg/day for β-HCH and δ-HCH; and 0.002 μg/kg/day for γ-HCH. In the Total Diet Study conducted by FDA in 1990 on 936 food items, γ-HCH was detected in 23 items, while α-HCH and β-HCH (combined) were detected in 11 items. Information on the amount of levels found were not provided (Yess 1991). The average concentration of lindane in 234 ready-to-eat foods was 0.0012 μg/g (KAN-DO Office and Pesticides Team 1995).

Studies in which soils containing 10 ppm radiolabeled γ-HCH were added to human skin samples at a quantity that exceeded complete coverage (5 mg soil / cm^2 skin) demonstrated mean γ-HCH absorptions of 1.04% from sandy soils and 1.64% from silt soils (Duff and Kissel 1996). However, data from soil absorption studies can vary due to factors such as the amount of soil added to skin, the exposure time, and possible evaporation of the contaminant.

The results of biomonitoring studies can be used as indicators of human exposures to HCH. The National Human Adipose Tissue Survey (NHATS) conducted in 1982 showed that β-HCH (the most prevalent HCH isomer in fatty tissue) was detected in 87% of 46 composite samples at <19–570 ng/g (ppb) concentrations (Stanley 1986). It was detected most often in postmortem samples collected from individuals from the southern United States. In another survey conducted in 1970–1975, β-HCH was detected in more than 90% of the postmortem human adipose tissue samples at an average level of 300 ppb (Kutz et al. 1979). In a review of the NHATS data available from 1970 to 1983, Mack and Mohadjer (1985) reported that the estimated 1983 national median level of β-HCH was 80 ppb, in comparison to the historic level of 140 ppb. The median level has decreased over time, but the compound has continued to be detected in nearly 100% of the population surveyed. Median levels are highest in the South census region and tend to increase with age

but have not been found to differ across the sexes or racial groups. A further analysis of the NHATS data indicated that average β-HCH concentrations in fat had decreased from 0.45 ppm in 1970 to approximately 0.16 ppm since 1981 (Kutz et al. 1991).

A comparison of the levels of α-HCH and β-HCH in the whole blood and biopsy fat of 25 patients showed median levels of 0.04 ng/g (maximum, <0.04 ng/g) and 0.13 ng/g (maximum, 2.60 ng/g) for the blood and 1.1 ng/g (maximum, 9.6 ng/g) and 18.0 ng/g (maximum, 748.6 ng/g) for the fat tissue, respectively (Mes 1992). A further comparison of β-HCH levels in breastmilk and adipose tissue samples was made for populations living near the Great Lakes (Canada only) and in other Canadian regions. Mean β-HCH levels in breast milk (0.6 ng/g) and adipose tissue (23.4 ng/g) were lower near the Great Lakes than in other parts of Canada (0.8 ng/g and 30.8 ng/g, respectively) (Mes and Malcolm 1992). Levels of HCHs in the adipose tissue of Japanese males increased from the late 1940s to 1966, coinciding with an increased annual production of HCH (Loganathan et al. 1993). Levels have been dropping since HCHs were banned in 1971, from a maximum level of 28 μg/g to present levels of less than 1 μg/g. Since 1974, only the more persistent β-HCH isomer has been found (Loganathan et al. 1993).

γ-HCH was one of the most frequently detected pesticides in the blood of Virginia residents, although the number of individuals sampled was not identified (Griffith and Blanke 1975). γ-HCH blood concentrations were the highest in residents of the middle age group (41–60 years). Some of the frequency of γ-HCH occurrence in the state was attributed to its common use in commercial vaporizers and its presence in cigarette smoke (Griffith and Blanke 1975). The National Health and Nutrition Examination Survey (NHANES) analyzed blood and urine specimens for the presence of HCH isomers. β-HCH was detected in approximately 13.9% of the U.S. population (12–74 years) in the Northeast, Midwest, and South. The median level for the 91% quantifiable positive results was 1.7 ppb (Murphy and Harvey 1985).

Factors such as age, dietary habits, and residence can influence the body burden of γ-HCH in exposed individuals. In one study, it was shown that women between the ages of 26 and 34 years who lived in a rural area of India and were nonvegetarians tended to show higher body levels of γ-HCH than other Indian women who lived in an urban area or who were vegetarians (Saxena et al. 1981a). The higher levels of γ-HCH in women at an older child-bearing age suggest that a longer life span may cause a greater accumulation of pesticide in the body. Higher pesticide levels are found in mutton, eggs, and chicken which are common in nonvegetarian meals; therefore, there tends to be a higher level of γ-HCH in the bodies of nonvegetarians. Individuals living in rural areas are more likely to be exposed to γ-HCH because agricultural fields are the

primary site of application of pesticides. In addition, studies indicate that γ-HCH is also present in breastmilk at an average level of 0.006 ppm in Alberta, Canada (Currie et al. 1979). In a study of 50 donors of breastmilk in Oahu, Hawaii, Takahashi et al. (1981) demonstrated HCH in 82% of the samples at a mean level of 81 ppb within a range of 0–480 ppb, expressed in terms of extractable lipid.

A study conducted in Colorado indicated, in general, that no quantitative relationships were demonstrated between pesticide levels in household dust and pesticide levels in blood. However, γ-HCH levels in blood sera in a pesticide formulator (16.8 ppb) and his wife (5 ppb) were found to be elevated in a household in which dust levels measured 5.85 ppb (Starr et al. 1974). It is possible that the γ-HCH found in the wife's blood and in the household came from the clothes and person of the pesticide formulator.

The Nonoccupational Pesticide Exposure Study (NOPES) conducted by EPA was based on the Total Exposure Assessment Methodology (TEAM) approach to exposure estimation. NOPES was designed to provide estimates of nonoccupational exposure to 32 household pesticides in the United States. Samples were collected at two locations: (1) Jacksonville, Florida, an area representative of high pesticide usage; and (2) Springfield/Chicopee, Massachusetts, an area of low-to-moderate pesticide usage. Detectable levels of γ-HCH were found in the personal air samples of 32–70% of the Jacksonville sample population; the range of mean concentrations in the air samples was 7–22 ng/m^3. For the Springfield population, detectable levels of γ-HCH were found in personal air samples collected from 8% to 10% of the population, with mean concentrations of 0.7–5 ng/m^3 (EPA 1990c).

A study on occupational pesticide exposure of commercial seed-treating applicators was conducted in Montana (Grey et al. 1983). No exposure was detectable on the chest and arm pads, but γ-HCH was detected on the hands and on the respirator pads. Workers involved with γ-HCH application complained of nasal irritation if they did not wear a respirator or mask. The α-, β-, γ-, and δ-isomers of HCH have been detected in the blood serum and adipose tissue of individuals occupationally exposed to HCH in pesticide formulation. Serum levels of <0.5 ppb–1 ppm α-HCH, <0.9 ppb–0.72 ppm β-HCH, <0.7 ppb–0.17 ppm γ-HCH, and 0.002–0.16 ppm δ-HCH have been detected in exposed workers (Baumann et al. 1980; Kashyap 1986; Morgan and Lin 1978; Nigam et al. 1986). Mean adipose tissue levels of 5.8 mg α-HCH/kg, 45.6 mg β-HCH/kg, and 3.1 mg γ-HCH/kg have also been reported in exposed workers (Baumann et al. 1980).

In general, accidental or intentional ingestion would lead to the highest exposures. Worker exposure constitutes the next highest exposure population although worker exposure is decreasing in both the number

of workers exposed and the levels of exposure. Lastly, the general population receives the lowest levels, which occur mainly from ingestion of foods and water with γ-HCH residues. Living near a waste disposal site contaminated with γ-HCH will also increase the likelihood of exposure.

5.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans and briefly considers potential pre-conception exposure to germ cells. Differences from adults in susceptibility to hazardous substances are discussed in 2.6 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, and breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, they put things in their mouths, they may ingest inappropriate things such as dirt or paint chips, they spend more time outdoors. Children also are closer to the ground, and they do not have the judgement of adults in avoiding hazards (NRC 1993).

Prenatal exposure of children to HCH can occur. β- HCH and γ-HCH have been found in samples of human maternal adipose tissue, maternal blood, cord blood, and breastmilk in women who were exposed to unknown levels of various organochlorine pesticides in Kenya (Kanja et al. 1992). Placental transfer of HCH in humans has been well documented (Saxena et al. 1981). Higher levels of total HCH and lindane were found in specimens of maternal blood, placenta, and umbilical-cord blood from women experiencing premature labor, spontaneous abortions, and stillbirths when compared to matched controls (Saxena et al. 1980; Saxena and Siddiqui 1983). Saxena et al. (1980) reported HCH levels of 69.3–550.4 ppb and γ-HCH levels of 30.8–113.6 ppb in the blood of women in India who had experienced spontaneous abortions or premature labor compared with blood HCH levels of 22.2–85.5 ppb and γ-HCH levels of 7.1–32.5 ppb in women who had undergone full-term pregnancy. Serum levels of a number of other pesticides including aldrin, DDE, DDT, and DDD were also found to be higher in cases of premature labor and spontaneous abortions. It was, therefore, not possible to establish a causal relationship between the serum HCH levels and these adverse effects. However, HCH has been shown to accumulate in amniotic fluid, placenta, and fetal tissues after treatment of pregnant mice (Srivastava and Raizada 1993) and can be related to fetolethality.

HCH is commonly detected in low concentrations (0.015 mg/kg fat) in the breastmilk of women exposed to HCH in the environment (Fytianos et al. 1985). Levels of HCH isomers in breastmilk have been reported, particularly in developing countries that still use HCH as a pesticide. Studies indicate the γ-HCH is present in breastmilk at an average level of 6 ppb in Alberta, Canada (Currie et al. 1979). In a study of 50 donors of breastmilk in Oahu, Hawaii, Takahashi et al. (1981) demonstrated HCH in 82% of the samples at a mean level of 81 ppb within a range of 0–480 ppb, expressed in terms of extractable lipids. Breastmilk concentrations of α-, β -, γ-, and δ-HCH were determined from samples obtained from two areas of India that were under malaria control (Dua et al. 1997). The mean concentrations of α-, γ-, β-, and δ-HCH in one area were 0.002, 0.002, 0.022, and 0.001 (mg/kg) , while in the second area concentrations were 0.003, 0.006, 0.078, and 0.002, respectively. Another study performed in a different region of India also demonstrated the presence of HCH isomers in breastmilk (Nair et al. 1996). Mean breastmilk concentrations of α-, β-, and γ-HCH were 0.045, 0.198 and 0.084 (mg/L), respectively. δ-HCH was not detected in the breastmilk samples. In a study designed to quantify the levels of organochlorine residues in the breastmilk of mothers in Uganda, Africa, the milk fat concentrations of α- HCH, β-HCH and γ-HCH ranged from 0.006–0.46, 0.005–0.25 and 0.01–0.87 mg/kg, respectively (Ejobi et al. 1996). The concentration of β-HCH in breastmilk samples from 3 regions in the Czech Republic ranged from 71 to 80 ng/g (Schoular et al. 1996). A comparison of β-HCH levels in breastmilk and adipose tissue samples was made for populations living near the Great Lakes (Canada only) and the rest of Canada. Mean β-HCH levels in breastmilk (0.6 ng/g) and adipose tissue (23.4 ng/g) were lower near the Great Lakes than in other parts of Canada (0.8 ng/g and 30.8 ng/g, respectively) (Mes and Malcolm 1992).

As mentioned previously, exposures to HCH can result from the ingestion of plants, animals, animal products, milk, and water containing the pesticide. A smaller degree of exposure may result from ingestion of drinking water containing HCH. There is also the possibility of exposure to γ-HCH from medical usage (e.g., shampoos for control of lice and lotion for treatment of scabies). Numerous studies have documented the effects in humans overexposed to γ-HCH through misuse or accidental ingestion of products used to treat head lice (Davies et al. 1983; Jaeger et al. 1984; Lee and Groth 1977). Although some controversy exists as to whether γ-HCH is a safe therapeutic agent when used in accordance with the manufacturers' guidelines, it is clear that most exposures occur through misuse of products (Rasmussen 1980, 1981, 1987). Besides medical usage, children are likely to be exposed to HCH from the ingestion of food containing the pesticide. Based on FDA's Total Diet Analyses, γ-HCH intakes (body weight/day) are 0.8 µg/kg for 6-11-month-old infants, 7.9 µg/kg for 2-year-old toddlers, and 1.4 and 3.1 µg/kg for 14–16-year-old males and females, respectively (FDA 1989b). HCH isomers have been detected in the following food types formulated for

infants and toddlers: whole milk and other dairy products; meat, fish, and poultry; oils and fats; vegetables; and sugars and adjuncts (Gartrell et al. 1986a).

HCH isomers have also been detected in cow's milk in those countries that still use the chemical as a pesticide. In a study performed in Uganda, Africa, the concentrations of α- HCH, β-HCH and lindane in cow's milk were 0.002–0.014, 0.003–0.018, and 0.006–0.036 mg/kg milkfat, respectively (Ejobi et al. 1996). Mean levels of HCH isomers analyzed in cow's milk samples from 2 separate areas in India were 0.0045 and 0.012 mg/kg α-HCH, 0.002 and 0.015 mg/kg γ-HCH, 0.0105 and 0.028 mg/kg β-HCH and 0.002 and 0.003 mg/kg δ-HCH (Dua et al. 1997). A monitoring study of 192 samples of cow's milk from Mexico revealed 0.001–0.201 mg/kg α-HCH, 0.008–0.253 mg/kg β-HCH and 0.002–0.187 mg/kg γ-HCH (Waliszewski et al. 1996). HCH isomers have also been detected in buttermilk and butter prepared from cow's milk contaminated with these isomers (Sreenivas et al. 1983).

HCH is bioavailable from soil and can be absorbed both orally and dermally (Duff and Kissel 1996). γ-HCH exhibited mean 24-hour dermal absorption values from 0.45 to 2.35% varying with different soil types and soil loadings of 1, 5, and 10 mg/cm^3. Some children intentionally eat dirt and most inadvertently ingest dirt by putting fingers or other objects in their mouths while playing outdoors. Thus, they are more likely than adults to be exposed to HCH via ingestion or direct contact of soil contaminated with HCH.

Children may also be exposed to a significant amount of HCH from household dust; parents' work clothes, skin, hair, tools, and other objects removed from the workplace are a likely source of exposure to children. An analysis of environmental contribution to pesticide body burden indicated household dust can be a major source of environmental HCH exposure (Starr et al. 1974), as indicated by elevated γ-HCH levels in blood sera in a pesticide formulator (16.8 ppb) and his wife (5 ppb) in a household in which dust levels measured 5.85 ppb. It is possible that the γ-HCH found in the wife's blood and in the household came from the clothes and person of the pesticide formulator.

γ-HCH is a restricted use pesticide. Its registered use around the home is limited to structural treatment, dog shampoo, and dog dust for fleas and ticks. Children can be exposed at home because of its potential use on pets and improper or illegal pesticide application.

Analyses of blood samples of 186 children living in an area contaminated with HCH, which was used as an insecticide in Brazil, revealed the presence of α-, γ-, and β-, HCH isomers (Brilhante and Oliveira 1996).

The authors reported that 24% of the children showed 0.89 ppb average concentrations of β-HCH in the blood. α- and γ-isomers were detected in only 3 and 1 children, respectively, at a mean concentration of 1.8 ppb and 0.95 ppb, respectively.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The populations with the most potential for chronic exposure to HCH are workers who either manufacture or routinely use these isomers. Exposure of the general population to γ-HCH tends to be low because federal regulations limiting its use have taken effect. However, γ-HCH is available in some consumer products (e.g., shampoos, food) and medications, and the possibility of exposure from these products is a source of concern. Individuals living near hazardous waste sites contaminated with γ-HCH may also be exposed to the compound.

Numerous studies have documented the effects in humans overexposed to γ-HCH through misuse or accidental ingestion of products used to treat scabies and head lice (Davies et al. 1983; Jaeger et al. 1984; Lee and Groth 1977). Although some controversy exists as to whether γ-HCH is a safe therapeutic agent when used in accordance with the manufacturers' guidelines, it is clear that most exposures occur through misuse of products (Rasmussen 1980, 1981, 1987). In addition, other studies have described cases in which patients have shown neurotoxic effects following excess exposure or ingestion of pesticides (Harris et al. 1969; Hayes 1976; West 1967).

Exposure to the other isomers of HCH (as in the technical-grade HCH) is limited in the United States as a result of regulations restricting their use. However, persons traveling or living in areas where the use of HCH is legal (e.g., South America, Eastern Europe, and Asia) should be wary of exposure to isomers of HCH through food and drinking water sources (Krauthacker et al. 1986; Radomski et al. 1971a; Saxena et al. 1980, 1981a, 1981b).

5.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of hexachlorocyclohexane is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research

designed to determine the health effects (and techniques for developing methods to determine such health effects) of hexachlorocyclohexane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.8.1 Identification of Data Needs

Physical and Chemical Properties. Sufficient information is available on the physical and chemical properties of γ-HCH and the other HCH isomers (see Chapter 3) to permit an assessment of the environmental fate of these compounds. No additional studies are required at this time.

Production, Import/Export, Use, Release, and Disposal. Production methods for HCH are well described in the literature (IARC 1979). γ-HCH is used as an insecticide and as a therapeutic scabicide and pediculicide for treatment of ectoparasite in humans and animals (Budvari et al. 1989). The production and use of γ-HCH as a pesticide has been restricted in the United States, and the use of technical-grade HCH was voluntarily canceled in 1976 (EPA 1978). There is no current information on the import of γ-HCH, and there is no information on the import of other HCH isomers. This information will be helpful for estimating human exposure particularly of populations living near industrial and hazardous waste sites. Release of γ-HCH to environmental media has been primarily from its use as a pesticide. Wastes containing γ-HCH must be contained, incinerated, and disposed of in landfills (EPA 1991g). Carbon absorption or flocculation are useful treatment methods for the removal of HCH from aqueous effluent streams, except when methanol is also contained in the effluents (HSDB 1993). Disposal methods are currently subject to revision under EPA guidance.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1994, became available in

May of 1996. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. γ-HCH released to the environment partitions to the atmosphere, soils, and sediments (Atkins and Eggleton 1971; Lewis and Lee 1976; Melancon et al. 1986; Saleh et al. 1982; Stanley et al. 1971). The compound is transported in the atmosphere, surface water, and groundwater (Mackay and Leinonen 1975; Nordmeyer et al. 1992; Stanley et al. 1971). γ-HCH is transformed via biodegradation in soils and surface waters (Govind et al. 1991; Kar and Singh 1979b; Kennedy et al. 1990; Macholz and Kujawa 1985; Sharom et al. 1980; Tu 1976). Available data indicate that photodegradation or other degradation processes are not significant processes in the removal of γ-HCH from air, as compared to rain-out and dry deposition (Atkins and Eggleton 1971; Hamada et al. 1981). Additional information on the transport, transformation, and persistence of the compound in soils and groundwater, particularly at hazardous waste sites, would be useful in identifying the most important routes of human exposure to γ-HCH. There is information regarding the half-lives for γ-HCH in water (3–30 days, 30–300 days, and >300 days for river, lake, and groundwater, respectively [Zoetemann et al. 1980]), but not in air or soil. There is no information about the half-lives for the other HCH isomers in any environmental media. Environmental fate data on HCH isomers other than γ-HCH are scant. Additional data on the half-lives for γ-HCH in air and soil, and further environmental fate data for the other HCH isomers, would be helpful. These data could be used to estimate exposure to HCH under various conditions of environmental release for purposes of planning and conducting meaningful follow-up exposure and health studies.

Bioavailability from Environmental Media. Evidence of absorption following inhalation and dermal exposure is available for workers involved in the formulation of pesticide products containing HCH isomers and in the use of γ-HCH (Baumann et al. 1980; Grey et al. 1983). Dietary intake is a major route of exposure for the general population (Gunderson 1988). Additional information on the absorption of γ-HCH, following ingestion of foods containing residues of the compound, would be helpful. As mentioned in Section 5.3.1, Duff and Kissel (1996) showed that bioavailability of γ-HCH via dermal exposure depended upon levels of soil loading. Dermal absorption ranged from 0.45 to 2.35%. For populations living in the vicinity of hazardous waste sites, additional information on absorption following dermal contact with, or ingestion of, contaminated soil would also be helpful, given the expected strong sorption of the compound to soil particulates. Besides γ-HCH, other isomers of HCH have been detected in adult diet foodstuffs (Gartrell et al. 1986b). Additional information on the absorption of these other HCH isomers following ingestion of foods containing residues of these isomers would be helpful. Because of the potential of HCH to contaminate

air, drinking water, and soil, further information on the bioavailability of the HCH isomers from these environmental media would be useful for assessing possible health concerns for humans.

Food Chain Bioaccumulation. γ-HCH in surface waters and soils is taken up and bioconcentrated by terrestrial and aquatic organisms (Just et al. 1990; Matsumura and Benezet 1973; Ramamoorthy 1985; Verma and Pillai 1991; Viswanathan et al. 1988). γ-HCH is bioconcentrated to high levels following uptake from surface waters by a number of aquatic organisms (Matsumura and Benezet 1973; Ramamoorthy 1985; Schimmel et al. 1977). Uptake from soils and bioconcentration by plants and terrestrial organisms appears to be limited (Verma and Pillai 1991; Wild and Jones 1992). Limited information suggests that the compound is not biomagnified in terrestrial food chains because of its metabolism by terrestrial organisms (Schmitt et al. 1985). Bioconcentration values in zebra-fish for α-HCH and β-HCH are reported (Butte et al. 1991). Among the HCH isomers, β-HCH accumulates the most in the food chain (Szokolay 1977). Additional information on the potential bioaccumulation of α-, β-, and δ-HCH isomers in terrestrial and aquatic food chains would be helpful.

Exposure Levels in Environmental Media. Environmental monitoring data are available predominantly for γ-HCH in air (Atlas and Giam 1988; Knap and Binkley 1991), surface water (Sandhu et al. 1978; Staples et al. 1985), groundwater (Sandhu et al. 1978), soil (Carey et al. 1978; Staples et al. 1985), and foods (FDA 1989b; Gunderson 1988; Kutz et al. 1976). γ-HCH has been detected in air, surface water and groundwater, and sediment and soil. The widespread distribution of HCH isomers in air has been confirmed (Tanabe et al. 1982). Although the use of γ-HCH has been restricted and the use of technical-grade HCH was voluntarily canceled in 1976 (EPA 1978), it is not likely that new environmental measurements will show considerably lower levels of γ-HCH in these media since there are remaining impacts from importing and processing HCH. Therefore, additional information on the levels of γ-HCH and α-, β-, and δ-HCH isomers is needed to assess the current potential human exposure to the chemicals from environmental media, particularly near hazardous waste sites.

Reliable monitoring data for the levels of hexachlorocyclohexane in contaminated media at hazardous waste sites are needed so that the information obtained on levels of hexachlorocyclohexane in the environment can be used in combination with the known body burdens of hexachlorocyclohexane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. HCH can be detected in the blood (Baumann et al. 1980; Griffith and Blanke 1975; Murphy and Harvey 1985), urine (Murphy and Harvey 1985), adipose tissue (Baumann et al. 1980; Stanley 1986), breastmilk (Takahasi et al. 1981), and semen (Stachel et al. 1989) of exposed individuals. Most of the data on the body burden of HCH are from adipose tissue and blood serum analyses conducted postmortem or on occupationally exposed individuals. The disadvantage of using postmortem blood is that the HCH concentration may change after death. The occupational studies often do not report environmental levels; therefore, it is not possible to correlate body HCH levels with environmental levels. The results of the National Human Adipose Tissue Survey (NHATS) conducted in 1982 showed that β-HCH, the most prevalent isomer in fatty tissue, was detected most often in postmortem samples collected from individuals from the southern U.S. Additional information is needed on exposure to γ-HCH and α-, β-, and δ-HCH isomers in populations living in the vicinity of hazardous waste sites.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. The different pathways for exposure of children to HCH have been discussed in Section 5.6. Prenatal exposure of children to HCH has been demonstrated; it is well documented that placental transfer of HCH occurs, and HCH levels have been measured in placenta and cord blood in humans (Saxena et al. 1981; Nair 1996) and in amniotic fluid and fetal tissues in mice (Srivastava and Raijada 1993). Infants may also be exposed via ingestion of breastmilk and cow's milk. Exposure may also occur via ingestion of water containing HCH, food and animal products, and possibly through incidental ingestion of household dust. It has been demonstrated that household dust can be an important source of environmental HCH (Starr et al. 1974). This occurs especially if the parents work in facilities that process or use HCH and can bring home residues of HCH via their work clothes, skin, hair, tools, or other objects removed from the workplace. A take-home exposure study on pesticide applicators might be useful if such occupational exposure settings occur. Limited studies conducted on exposure of infants and children to γ-HCH from application of 1% γ-HCH lotion as scabicide indicated dermal absorption occurred (Ginsberg et al. 1977). Adipose tissue is a major storage depot for HCH. Although data from a national human adipose tissue survey exist (Stanley 1984), no quantitative data are currently available on the body burden of HCH in children. These studies are needed because unique exposure pathways for children exist, and children may be different from adults in their weight-adjusted intake of HCH because of their higher surface area to volume ratio and higher ingestion rate of household dust.

Exposure Registries. No exposure registries for hexachlorocyclohexane were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.8.2 Ongoing Studies

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, will be analyzing human blood samples for hexachlorocyclohexane and other volatile organic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

Biodegradability of HCH isomers and engineering applicability are being investigated in the Netherlands. Also, remedial investigations and feasibility studies at the NPL sites known to have γ-HCH contamination should add to the available database for environmental levels, environmental fate, and human exposure.

Ongoing studies concerning the environmental fate of HCH isomers have been identified as follows:

C.A. Reddy (Michigan State University) is currently examining a lignin-degrading filamentous fungus *(Phanerochaete chrysosporium)* to isolate, characterize, and develop expression/secretion systems for ligninases. These ligninases play a key role in lignin degradation and are also believed to be involved in the detoxification of γ-HCH. Similar studies on the biodegradation of γ-HCH by the white rot fungus are also being conducted by S.D. Aust at Utah State University.

W.F. Spencer (Agricultural Research Service, Riverside, California) is conducting studies in the laboratory and field to quantify the physical, chemical, and biological parameters related to rates of volatilization, degradation, and transport of γ-HCH and other chemicals into the atmosphere.

The effects of γ-HCH and 14 other insecticides on transformations of urea nitrogen (urea hydrolysis and nitrification) in 2 coarse-textured and 2 fine-textured soils are currently being examined by J.M. Brenner (Iowa State University).

M. Speedie and B. Pogell (University of Maryland) are investigating the metabolism of γ-HCH by streptomycetes. They have found degradative detoxification of 80% of γ-HCH added within 5 days; 60% is degraded by the end of the first 24 hours. The investigators assume that degradation occurs via a lignin peroxidase-mediated reaction.

R.W. Coble of the U.S. Geological Survey is conducting a study of the hydrology of an area containing six pesticide disposal sites near Aberdeen, Maryland. γ-HCH has been identified in water samples collected from several municipal wells in the area.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring hexachlorocyclohexane, its metabolites, and other biomarkers of exposure and effect to hexachlorocyclohexane. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

The α-, β-, γ-, and δ-isomers of HCH, and/or their phenolic metabolites have been measured in biological samples such as adipose tissue, serum, urine, milk, semen, and the brain by gas chromatographic methods listed in Table 6-1.

The most commonly used methods for measuring α-, β-, γ-, and δ-HCH in serum, semen, adipose tissue, and milk are gas chromatography (GC) or high-resolution gas chromatography (HRGC) combined with electron capture detection (ECD) and mass spectrometry (GC/MS) (Barquet et al. 1981; Burse et al. 1990; Butte and Fooken 1990; EPA 1980c; Gupta et al. 1978; LeBel and Williams 1986; Liao et al. 1988; Prapamontol and Stevenson 1991; Saady and Poklis 1990; Stachel et al. 1989; Waliszewski and Szymczynski 1983; Williams et al. 1988). The EPA GC/ECD method is capable of detecting γ-HCH and other HCH isomers in blood serum at the ppb level (EPA 1980c). Using HRGC, method detection limits for measuring HCH isomers in serum and milk are in the sub-ppm to low-ppb range (Butte and Fooken 1990; Prapamontol and Stevenson 1991; Saady and Poklis 1990); recovery and precision are acceptable (Butte and Fooken 1990; Prapamontol and Stevenson 1991; Saady and Poklis 1990). The use of capillary (high-resolution) GC enhances chromatographic separation of compounds with similar retention characteristics (Saady and Poklis 1990). Although GC has also been used in measuring the isomers in blood serum, recovery problems (i.e., low recoveries) have been encountered because of the volatility of the HCH isomers (Burse et al. 1990); sensitivity and precision data were not reported (Burse et al. 1990). GC/ECD combined with identification

Table 6-1. Analytical Methods for Determining Hexachlorocyclohexane in Biological Materials

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Urine	Hydrolyze sample; acidify; extract with hexane; derivatize for GC/ECD or evaporate to a small volume for TLC.	GC/ECD, TLC	Phenolic metabolites of γ-HCH	1 ppb (GC/ECD); 1 ppm (TLC)	95% NR	Balikova et al. 1988
Urine	Hydrolyze acidified sample; extract with diethyl ether; concentrate phenol conjugates	GC/ECD		4.9–18.6 ppb	87–119%	Angerer et al. 1981
Serum	Extract and concentrate serum using solid-phase extraction; elute with isooctane; inject	HRGC/ECD	α-HCH γ-HCH	0.18 ppm 0.33 ppm	70–75%	Saady and Poklis 1990
Serum	Extract serum with organic solvents; sample and acid cleanup on Florisil column; sample cleanup using silica gel chromatography	GC/ECD	β-HCH γ-HCH	NR NR	57.2–58.2% 47.7–50.4%	Burse et al. 1990
Serum	Extract with hexane	GC/ECD	α-HCH β-HCH γ-HCH	1 ppb 1 ppb 1 ppb	NR NR NR	EPA 1980a
Serum	Separate plasma from blood containing anticoagulant	GC/ECD	β-HCH	0.8 ppb	85%	Barquet et al. 1981
Serum	Hexane or hexane-acetone extraction	GC/ECD	α-HCH β-HCH γ-HCH	NR	82–83% 73–77% 90–96%	Gupta et al. 1978

Table 6-1. Analytical Methods for Determining Hexachlorocyclohexane in Biological Materials *(continued)*

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Semen	Liquid-liquid extraction; cleanup with Florisil	GC/ECD GC/MS(NCI)	α-BHC β-BHC	0.02 ppb 0.32 ppb	72.5% 94.7%	Stachel et al. 1989
Semen	Extract with acetic acid; cleanup with Florisil; elute with petroleum-diethyl ether	GC/ECD	α-BHC β-BHC γ-BHC δ-BHC	NR	86.3% 101.3% 951.0% 101.6%	Waliszewski and Szymczynski 1983
Adipose tissue	Extract with organic solvents; reextract lipids on Florisil column; elute with hexane and concentrate	GC/MS	α-BHC β-BHC	5–50 ppb	>100% 80–100%	Liao et al. 1988
Adipose tissue	Extract fat from tissue with acetone-hexane; fractionate from fat by gel permeation chromatography with methylene chloride-cyclohexane; cleanup on Florisil column; inject	HRGC/ECD GC/MS	α-BHC γ-BHC β-BHC	1.2 ppb 1.4 ppb 3.0 ppb	>89% >88% >91%	LeBel and Williams 1986
Adipose tissue	Grind sample; isolate fat, extract residue in petroluem ether	GC/ECD	α-HCH β-HCH γ-HCH	10 ppb 20 ppb 20 ppb	NR NR NR	EPA 1980a
	Grind tissue; extract with acetonitrile and acetone; evaporate; extract with hexane	GC/ECD	β-HCH	80 ppb	98%	Barquet et al. 1981

Table 6-1. Analytical Methods for Determining Hexachlorocyclohexane in Biological Materials *(continued)*

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Milk	Solvent extract with ethylacetate-methanol-acetone; cleanup and concentrate using solid-phase extraction; elute with isooctane	HRGC/ECD	α-HCH β-HCH γ-HCH	0.5 ppb 1 ppb 0.5 ppb	83–105% 91–119% 80–96%	Prapamontol and Stevenson 1991
Milk	Homogenize sample; extract and cleanup using silica gel; elute with hexane/dichloromethane; concentrate; inject	HRGC/ECD	α-HCH β-HCH γ-HCH	0.002 ppm 0.009 ppm 0.004 ppm	125% 114% 125%	Butte and Fooken 1990
Brain	Homogenize sample in hexane; centrifuge; inject	GC/MS (NCI)	γ-HCH and metabolites	3 pg/L	NR	Artigas et al. 1988b

α-BHC = alpha-hexachlorocyclohexane; β-BHC = beta-hexachlorocyclohexane; γ-BHC = gamma-hexachlorocyclohexane; δ-BHC = delta-hexachlorocyclohexane; ECD = electron capture detection; GC = gas chromatography; α-HCH = alpha-hexachlorocyclohexane; β-HCH = beta-hexachlorocyclohexane; γ-HCH = gamma-hexachlorocyclohexane; δ-HCH = delta-hexachlorocyclohexane; HRGC = high-resolution gas chromatography; MS = mass spectrometry; NCI = negative chemical ionization; NR = not reported; TLC = thin-layer chromatography

by GC/MS is a reliable method for quantitation and identification of HCH isomers in semen (Stachel et al. 1989); sensitivity of GC/ECD is in the sub-ppb range with acceptable recoveries (Stachel et al. 1989). HRGC/ECD and GC/MS have also been used for detection and identification of HCH isomers in adipose tissue (LeBel and Williams 1986; Liao et al. 1988). During sample preparation, the use of gel permeation chromatography is effective for separation of the isomers from adipose tissue (LeBel and Williams 1986). This method is sensitive (low- to sub-ppb range) and has good recoveries (>88%) and precision (#0.12% RSD). Although sensitivity is not quite as good as that of GC/ECD, GC/MS is more specific. GC/MS is usually used as a confirmatory method, but it can be reliably used alone and produces excellent recoveries and good precision (Liao et al. 1988).

γ-HCH and its metabolites have also been detected in brain tissue using GC/MS in the chemical ionization mode (Artigas et al. 1988a). The use of GC/MS with negative ion chemical ionization (NICI) is preferred over electron impact mass spectrometry (EIMS) because the sensitivity using NICI is orders of magnitude better than with EIMS. GC/MS with NICI is also more selective than GC/MS with EI or GC/ECD (Artigas et al. 1988a). Another advantage of GC/MS with NICI is that identification and quantitation are performed without any purification or extraction procedures (Artigas et al. 1988a).

The phenolic metabolites of γ-HCH and the other HCH isomers have been measured in urine samples using GC/ECD (Angerer et al. 1981; Balikova et al. 1988). Sensitivity for this method is in the low-ppb range and recovery is excellent (95%); however, precision was not reported (Balikova et al. 1988). Thin layer chromatography (TLC) has also been used in conjunction with GC/ECD for identification of HCH isomers (Balikova et al. 1988). Although TLC does not achieve the same sensitivity (ppm range) as GC/ECD, sensitivity can be increased by extraction of a larger volume of urine. The combination of GC and TLC was reported to be a reliable confirmation tool for identifying compounds (Balikova et al. 1988). Angerer et al. (1981) developed a sensitive and specific gas chromatographic method for the simultaneous detection of 10 chlorinated phenols that appear in the urine of individuals exposed to γ-HCH. However, the study authors noted that both HCH and chlorobenzene compounds are commonly used as pesticides and that both are metabolized to chlorophenols. This suggests that detection of these metabolites does not distinguish between HCH, chlorobenzene, or pentachlorophenol (PCP) exposure. Edgerton et al. (1979) detected chlorinated phenol metabolites of HCH and PCP in the urine of experimental animals and exposed individuals by using GC/ECD. Discrimination between HCH and PCP exposure was possible through comparisons of metabolite profiles. However, detection of PCP in the urine may also be an indication of exposure to PCP or other compounds similar to HCH.

6.2 ENVIRONMENTAL SAMPLES

HCH residues are present in the environment because γ-HCH is used as an insecticide on a wide variety of vegetables, fruits, field crops, and on uncultivated land. The most commonly used methods for measuring HCH isomers in environmental samples is GC or HRGC combined with ECD or MS. Table 6-2 presents details on selected analytical methods.

HCH isomers have been measured in air using GC/ECD, HRGC/ECD, or GC with dual detection by ECD and electrolytic conductivity detection (ELCD) (Durell and Sauer 1990; Kurtz and Atlas 1990; NIOSH 1984; Stein et al. 1987; Zaranski et al. 1991). Polyurethane foam or Florisil adsorbent tubes are suitable for collecting air samples. The use of a simultaneous dual-column, dual-detector method (ECD and ELCD) was found to reduce the risk of false positive identifications without increasing the cost or time of analysis (Durell and Sauer 1990). Both columns were able to separate a large number of analytes with good reproducibility. Although ECD is more sensitive for halogenated compounds and has a lower detection limit (sub-ppb to low-ppm) than ELCD (low ppb), ELCD can greatly reduce matrix interferences. Precision and recovery were not reported for either detector (Durell and Sauer 1990; Kurtz and Atlas 1990).

The most commonly used methods for detecting HCH isomers in water (e.g., surface water, drinking water, sea water, groundwater, waste water, and rain) include GC or HRGC combined with ECD or MS (Allchin 1991; Barquet et al. 1981; Durell and Sauer 1990; EPA 1984, 1986a; Goosens et al. 1990; Kurtz and Atlas 1990; Lopez-Avila et al. 1989a, 1990b; Reding 1987; van der Hoff et al. 1991). To improve sample extraction and cleanup, the most current EPA method (Method 8120) used commercially available disposable Florisil cartridges instead of conventional Florisil cleanup (Lopez-Avila et al. 1989a). The disposable Florisil cartridges were simpler to use, shortened the analysis time, and reduced the overall cost of the analysis. The excellent precision, accuracy, and sensitivity (ppt range) of the results indicated that the revised method is reliable (Lopez-Avila et al. 1989a). Automated solid-phase extraction cartridges filled with silica and coupled on-line to GC/ECD have been effectively used to measure HCH isomers in water at low levels (ppt) (van der Hoff et al. 1991). This method is efficient and reproducible, with good recovery (>95%) and precision (<12% coefficient of variance (CV)) (van der Hoff et al. 1991). On-line liquid-liquid extraction coupled with HRGC/ECD is also a sensitive (ppb level) and reliable method (Goosens et al. 1990). A method validation study, conducted on EPA Method 508, for determining HCH isomers in finished drinking water using GC/ECD indicated the method was reliable, repeatable, and reproducible (Lopez-Avila et al. 1990b). Precision was good; recovery (>90%) was excellent. Sensitivity was in the ppb range (Lopez-Avila

Table 6-2. Analytical Methods for Determining Hexachlorocyclohexane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Air	Collect air using filters and polyurethane foam; Soxhlet extraction; column cleanup and isolation; concentration; dual column detection	HRGC/ECD HRGC/ELCD		0.9 pg/μL 15.3 pg/μL	NR NR	Durell and Sauer 1990
Air	Collect sample in Florisil adsorbent tubes; elute with methylene chloride in pentane; concentrate in Kuderna-Danish evaporative concentrator; solvent exchange to hexane	HRGC/ECD		low pg/m^3	NR	Kurtz and Atlas 1990
Air	Trap in isooctane	GC/ECD		3 μg/sample	NR	NIOSH 1984 (Method 5502)
Air	Adsorb air sample on florisil; elute with 10% 2-propanol in hexane	GC/ECD	α-BHC β-BHC γ-BHC δ-BHC	0.25 pg/m^3	83% 88% 81% 87%	Stein et al. 1987
Surface water	Extract with hexane; concentrate; cleanup using automated solid-phase extraction technique	GC/ECD	α-HCH β-HCH γ-HCH δ-HCH	7 ppt 10 ppt 7 ppt 6 ppt	95.6% 98.2% 95.6% 95.9%	van der Hoff et al. 1991

Table 6-2. Analytical Methods for Determining Hexachlorocyclohexane in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Water	Extract twice with methylene chloride; dry with anhydrous sodium sulfate; concentrate; add hexane and concentrate by evaporation; cleanup on disposable Florisil cartridge and elute with hexane-acetone	GC/ECD	α-HCH β-HCH γ-HCH δ-HCH	11 ppt 31 ppt 23 ppt 20 ppt	96% 103% 96% 103%	Lopez-Avila et al. 1989a (Modified EPA Method 8120)
Drinking water	Extract with methylene chloride; solvent exchange to methyl ter-butyl ether; concentrate	GC/ECD	α-HCH β-HCH γ-HCH δ-HCH	0.025 ppb 0.010 ppb 0.010 ppb 0.015 ppb	94.6% 93.4% 94.2% 92.0%	Lopez-Avila et al. 1990b (EPA Method 508)
Drinking water	Stripping for water with an inert gas-helium	HRGC/ECD		0.003 ppb (Method 505); 0.006 ppb Method 508)	93–130%	Reding 1987 (EPA Methods 505, 508)
Drinking water	Separation with Na_2SO_4; extraction with CH_2Cl_2	GC/ECD	β-HCH	0.025 ppb	88%	Barquet et al. 1981
Water and waste water	Extraction with methylene chloride	GC/ECD	α-HCH β-HCH γ-HCH δ-HCH	0.003 ppb 0.006 ppb 0.004 ppb 0.009 ppb	NR NR NR NR	EPA 1984 (Method 608)

Table 6-2. Analytical Methods for Determining Hexachlorocyclohexane in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Water and waste water	Extraction with methylene chloride	GC/MS	β-HCH δ-HCH	4.2 ppb 3.1 ppb	NR NR	EPA 1984 (Method 625)
Water and waste water	Extraction with methylene chloride	GC/ECD	α-HCH β-HCH γ-HCH δ-HCH	0.003 ppb 0.006 ppb 0.004 ppb 0.009 ppb	NR NR NR NR	EPA 1986e (Method 8080)
Sea water	Extract twice with hexane; dry over anhydrous sodium sulfate; concentrate; cleanup using column chromatography with 5% deactivated alumina; concentrate	GC/ECD	α-HCH, γ-HCH	1 ppt	>85%	Allchin 1991
Ground-water	On-line liquid-liquid extraction of sample with isooctane and separation of aqueous and organic phases by a sandwich phase separator	HRGC/ECD	α-HCH δ-HCH	0.1 ppb	112% 119%	Goosens et al. 1990
Sea water, rain (lindane)	Liquid-liquid extraction; column cleanup and isolation; concentration	HRGC/ECD HRGC/ELCD		0.9 ppb 15.3 ppb	NR NR	Durrell and Sauer 1990

Table 6-2. Analytical Methods for Determining Hexachlorocyclohexane in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Sea water	Extract with methylene chloride; solvent exchange to hexane; cleanup on Florisil	HRGC/ECD	α-HCH, γ-HCH	low pg/L	NR	Kurtz and Atlas 1990
Soil	Extract with supercritical carbon dioxide or carbon dioxide modified with 10% methanol	GC/ECD GC/MS	α-BHC β-BHC γ-BHC δ-BHC	NR	77.43–93.6% 79.28–93.6% 80.63–121% 72.4–103%	Lopez-Avila et al. 1990
Soil	Dry sample with anhydrous sodium sulfate; extract twice with methylene chloride-acetone by sonication; filter; dry; concentrate; cleanup on disposable Florisil cartridge and elute with hexane-acetone	GC/ECD	α-HCH β-HCH γ-HCH δ-HCH	<40 ng/L	96% 103% 96% 103%	Lopez-Avila et al. 1989b (Modified EPA Method 8120)
Soil (lindane) (lindane)	Equilibrate with water; extract with acetone and hexane (1:1); wash with water and sodium chloride desiccate with anhydrous sodium sulfate; concentrate; add hexane; cleanup with SPE Florisil cartridge.	GC		5 ppm	108%	Noegrohati and Hammers 1992

Table 6-2. Analytical Methods for Determining Hexachlorocyclohexane in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Soil, sediment, waste sludge	Extract sample with methylene chloride-acetone by sonication; clean up using gel permeation chromatography processing of extracts dissolved in 1+1 butyl chloride-methylene chloride or 100% methylene chloride	HRGC/ECD, HRGC/MS	γ-BHC	NR	83–91%	Czuczwa and Alford-Stevens 1989
Soil	Hexane-acetone extraction	GC/ECD		NR	NR	AOAC 1984 (Method 29.013)
Soil	Extraction with methylene chloride followed by clean-up on Florisil column	GC/ECD, HSD	α-HCH β-HCH δ-HCH δ-HCH	3.0 ppm 6.0 ppm 4.0 ppm 9.0 ppm	NR NR NR NR	EPA 1986e (Method 8080)
Sediment	Extract using vapor phase distillation technique; dry isooctane extract; concentrate	GC/ECD	α-HCH γ-HCH	2.42 ppb 4.98 ppb	76% 40%	Schuphan et al. 1990
Milk	Selective extraction of HCH isomers on solid-matrix disposable column by means of acetonitrile-saturated light petroleum; concentrate; cleanup extract on Florisil minicolumn	GC/ECD	α-HCH γ-HCH β-HCH	NR	94% 105% 113%	DiMuccio et al. 1988

Table 6-2. Analytical Methods for Determining Hexachlorocyclohexane in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Milk	Extract fortified milk samples with acetone and n-hexane; centrifuge; evaporate organic phase; dissolve residues in ether	GC/ECD	α-HCH β-HCH γ-HCH δ-HCH	NR	95.7% 99.9% 83.4% 89.7%	Kapoor et al. 1981
Soil, water, wheat, rice, beans	Extract BHC from sample by activated charcoal; dechlorination of BHC to benzene; nitration of benzene to m-dinitro-benzene; reduction to m-phenylene diamine; diazotization and coupling to form azo dye	Spectrophoto-metry	γ-HCH	NR	≥89%	Raju and Gupta 1988
Mussels (lindane)	Extract with acetonitrile; separate from coextractives by liquid-liquid partition between acetonitrile and water/hexane; cleanup on Sep-Pak Florisil cartridge; elute in second eluate with 15% ethyl ether in hexane	GC/ECD		0.02 µg/kg	92–102%	Muino et al. 1991
Fish (lindane)	Extract residue using one-step matrix solid phase dispersion combined with Florisil column cleanup; inject into GC	GC/ECD		10 ng/g	82%	Long et al. 1991a

Table 6-2. Analytical Methods for Determining Hexachlorocyclohexane in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Fish	Petroleum ether extraction	GC/ECD		NR	NR	AOAC 1984 (Method 20.029)
Fish (lindane)	Combine with anhydrous Na_2SO_4; extract with petroleum ether/ethyl acetate; separate lipids with GPC; solvent exchange to iso-octane; add dry N_2 gas	GC/MS (NCI)		1.6 ppb	115%	Schmidt and Hesselberg 1992
Fruits and vegetables	Extract samples with acetonitrile; partition with sodium chloride saturated aqueous solution; concentrate	HRGC/MS	α-BHC β-BHC γ-BHC δ-BHC	0.05 µg/g (all isomers)	88% 93% 93% 112%	Liao et al. 1991
Vegetables (lindane)	Extract with methanol; and partition with sodium chloride and hexane; wash hexane layer with sodium chloride solution; desiccate with anhydrous sodium sulfate; concentrate; cleanup on SPE Sil-Florisil cartridge	GC		ppb range	87–137%	Noegrohati and Hammers 1992

Table 6-2. Analytical Methods for Determining Hexachlorocyclohexane in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Beef fat (lindane)	Extract residue using one-step matrix solid phase dispersion combined with Florisil column cleanup; inject into GC	GC/ECD		low ppb	85%	Long et al. 1991b
Animal fat and dairy products	For dairy products, extract fat with hexane; for animal fat, melt sample and remove fat; cleanup with gel permeation chromatography; further cleanup with Florisil if necessary; inject	GC/ECD	BHC	low to sub ppm	82%	Venant et al. 1989
Root vegetables and dairy products	Extract with CO_2 collect with *n*-hexane; evaporate; add *n*-hexane; load on Florisil column; elute with 1:1 (v/v) *n*- hexane/dichloromethane; evaporate; dissolve in *n*-hexane	GC/ECD	α-HCH γ-HCH	NR NR	10–100% 12–98%	Bernal et al. 1992
Beef	Extract with acetone-hexane; cleanup on Florisil column; inject	GC/ECD	β-BHC	sub ppm	78.1–88.3%	Tonogai et al. 1989

Table 6-2. Analytical Methods for Determining Hexachlorocyclohexane in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Isomer	Sample detection limit	Percent recovery	Reference
Tobacco	Soak in acetonitrile water mixture, extract with petroleum ether; shake with H_2SO_4	GC/ECD	α-HCH β-HCH γ-HCH δ-HCH	1.0 ppm 2.0 ppm 2.0 ppm 2.0 ppm	98.2% 92.9% 96.2% 88.2%	Waliszewksi and Szymczynski 1986
Wood (rasped)	Extract with toluene; sonify and centrifuge; inject	GC-MS		10 ppb	NR	Butte and Walker 1992

α-BHC = alpha-hexachlorocyclohexane; β-BHC = beta-hexachlorocyclohexane; γ-BHC = gamma-hexachlorocyclohexane; δ-BHC = delta-hexachlorocyclohexane; CH_2Cl_2 = methylene chloride; ECD = electron capture detection; ELCD = electrolytic conductivity detector; GC = gas chromatography; GPC = gas permeation chromatography; α-HCH = alpha-hexachlorocyclohexane; β-HCH = beta-hexachlorocyclohexane; γ-HCH = gamma-hexachlorocyclohexane; δ-HCH = delta-hexachlorocyclohexane; H_2SO_4 = sulfuric acid; HRGC = high-resolution gas chromatography; HSD = halogen specific detector; MS = mass spectrometry; Na_2SO_4 = sodium sulfate; NCI = negative chemical ionization; NR = not reported; SPE = solid phase extraction

et al. 1990b). The EPA-established analytical test procedures to analyze water, waste water, and drinking water samples use GC coupled with MS. EPA methods 608 and 625 are recommended to detect γ-HCH and other HCH isomers in surface water and municipal and industrial discharges (EPA 1984).

GC/ECD, HRGC/ECD, and HRGC/MS are the most commonly used methods to measure HCH isomers in soil, sediments, and solid wastes (AOAC 1984; Czuczwa and Alford-Stevens 1989; EPA 1986b; Lopez-Avila et al. 1989b, 1990a; Noegrohati and Hammers 1992b; Schuphan et al. 1990). More efficient extraction of the isomers from soil was obtained using a disposable Florisil cartridge (modified EPA Method 8120) prior to detection by GC/ECD (Lopez-Avila et al. 1989b). The method yielded excellent recoveries (>95%), and sensitivity was in the ppt range. Sample cleanup using a disposable solid phase extraction (SPE) cartridge with detection by GC yielded a higher recovery (108%) with excellent precision (4% CV). Although sample detection limits were not reported, sensitivity was in the ppm range (Noegrohati and Hammers 1992b). Sample cleanup using gel permeation chromatography and detection and identification by HRGC/ECD and HRGC/MS resulted in good recoveries (83–91%) and good precision (#5.1% relative standard deviation [RSD]) (Czuczwa and Alford-Stevens 1989); sensitivity was not reported (Czuczwa and Alford-Stevens 1989). A new technique, supercritical fluid extraction (SFE), has been applied to the analysis of soil samples (Lopez-Avila et al. 1990a). Recovery (>75%) and precision (<26% CV) are adequate. Because this is a relatively new method, the cost is higher than other accepted techniques. The vapor phase extraction technique has also been applied to the analysis of trace residues of HCH in sediments (Schuphan et al. 1990). The efficiency of this method was compared with conventional Soxhlet extraction and Florisil cleanup procedures. The results showed that recovery using the Soxhlet extraction method (73–81%) was better than with vapor-phase extraction (40–76%). The low recovery of γ-HCH (40%) was due to sample loss during concentration of the iso-octane extract (Schuphan et al. 1990); sensitivity was in the low-ppb range; precision was excellent (0.01–0.03% coefficient of variation).

GC/ECD and HRGC/ECD are the most commonly used methods for measuring HCH isomers in milk (DiMuccio et al. 1988; Kapoor et al. 1981), dairy products (Bernal et al. 1992; Venant et al. 1989), seafood (mussels and fish) (AOAC 1984; Long et al. 1991a; Muino et al. 1991; Schmidt and Hesselberg 1992), fruits and vegetables (Liao et al. 1991; Noegrohati and Hammers 1992), beef (Tonogai et al. 1989), and beef fat (Long et al. 1991b). Gel permeation chromatography is a suitable method for the cleanup of HCH residues in animal fats and dairy products (Venant et al. 1989); recoveries are good (82%). Although specific detection limits were not reported, sensitivity is in the low-to-sub-ppm range. Additional cleanup with Florisil is needed when residue levels are below 0.1 ppm; precision was not reported. High-pressure soxhlet extraction

coupled with Florisil column cleanup yielded recoveries up to 100% for α-HCH and γ-HCH in butter, if pressure, time, and sample volume in the extractor were optimized; detection limits and precision values were not reported. This method has also been used to detect γ-HCH residues in potatoes with similar recoveries (Bernal et al. 1992). A reliable and reproducible method has been developed to determine HCH residues in milk (DiMuccio et al. 1988). The procedure involves a single-step, selective extraction of residues from milk on a solid-matrix disposable column, clean-up with Florisil, and detection by GC/ECD. Although specific detection limits were not reported, sensitivity is in the low-ppb range. With this extraction procedure, the HCH residues are more readily extracted than milk lipids, and the addition of a small amount of acetonitrile to the milk significantly improved recoveries without increasing the amount of fat in the extracts (diMuccio et al. 1988). A reliable, rapid screening technique for extraction of residues from a complex biological matrix such as fat uses matrix solid-phase dispersion (MSPD) extraction, Florisil column cleanup, and detection by GC/ECD (Long et. al. 1991a, 1991b). This method has been used to measure HCH residues in beef fat and fish. Recovery (82–85%) is good; sensitivity is in the low-ppb range. The MSPD method overcomes many of the complications associated with traditional pesticide isolation techniques because it uses small sample volumes and involves few steps (Long et al. 1991a, 1991b). GC/MS with negative ion chemical ionization (NCI) with GPC cleanup is a rapid, accurate, and simple method to quantify γ-HCH in fish. Recoveries were excellent (115%) with good precision (8.9% RSD), and a detection limit of 1.6 ppb (Schmidt and Hesselberg 1992). An HRGC/MS screening method has been developed for the determination of pesticide residues in a variety of crop samples (fruits and vegetables) (Liao et al. 1991). This technique is a useful tool because it offers simultaneous detection and confirmation, which are not provided by ECD. This method, however, lacks the sensitivity achieved by ECD. Spectrophotometry has been used to measure HCH isomers in cereals (e.g., wheat, rice, and beans) with good recoveries ($89%) (Raju and Gupta 1988). This technique has also been used for other matrices such as soil and water (Raju and Gupta 1988). An accurate and simple extraction and cleanup method has been developed for capillary GC analysis of γ-HCH in vegetables. The sample was extracted with methanol and cleanup was executed on disposable SPE cartridges. Recoveries ranged from 87% to 137% (average 100%) with good precision (CV # 5%). Although no specific detection limits were reported, sensitivity is expected to be in the ppb range (Noegrohati and Hammers 1992).

HCH residues have also been detected in tobacco using GC/ECD (Waliszewski and Szymczynski 1986). Sensitivity is in the low-ppm range and recovery is excellent (88–98%) (Waliszewski and Szymczynski 1986).

GC/MS has been used to determine γ-HCH residues in wood preserving fluids on the surface of wood; the detection limit is 10 ppb. No recovery or precision values were reported (Butte and Walker 1992).

6.3 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of hexachlorocyclohexane is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of hexachlorocyclohexane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Methods are available for measuring HCH residues and/or their metabolites in blood serum (Barquet et al. 1981; Burse et al. 1990; Gupta et al. 1978; EPA 1980c; Saady and Poklis 1990), urine (Angerer et al. 1981; Balikova et al. 1988), semen (Stachel et al. 1989; Waliszewski and Szymczynski 1983), adipose tissue (EPA 1980c; Barquet et al. 1981; LeBel and Williams 1986; Liao et al. 1988), breastmilk (Butte and Fooken 1990; Prapamontol and Stevenson 1991), and brain tissue (Artigas et al. 1988a). However, examination of blood and urine is most frequently conducted to determine exposure because of the ease of sample collection with these media. The available methods are accurate and reliable for most of the media. However, sensitivity and precision data for measuring HCH residues in serum are needed. Although available methods can detect and quantify background levels of HCH in the population, there is no information to quantitatively correlate levels in these fluids with exposure levels. Additional quantitative information regarding the relationship between body and environmental levels of HCH might allow investigators to predict environmental exposure levels from measured body levels.

Methods are available to detect the chlorinated phenol metabolites present in the urine as a result of exposure to HCH (Angerer et al. 1981; Balikova et al. 1988). However, similar metabolites are detected following exposure to other pesticides. The identification of a specific urinary metabolite of HCH alone (e.g., chlorophenol) would not allow investigators to determine whether an individual has been exposed to HCH.

The individual isomers of HCH can be detected in serum, urine, adipose tissue, and semen of exposed individuals as indicated above in Section 2.7.1 Biomarkers of Exposure and Effect. Since no quantitative correlation has been made between body levels of HCH and adverse health effects based on existing data, we do not know if the methods are sensitive enough to measure levels at which biological effects occur. Further studies need to be undertaken to quantitatively correlate body levels resulting from HCH exposure and the occurrence of specific adverse health effects.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods are available to detect HCH in air (Durell and Sauer 1990; Kurtz and Atlas 1990; NIOSH 1984; Stein et al. 1987; Zaranski et al. 1991), water (Allchin 1991; Barquet et al. 1981; Durell and Sauer 1990; EPA 1984, 1986a; Goosens et al. 1990; Kurtz and Atlas; Lopez-Avila et al. 1989a, 1990b; Reding 1987; van der Hoff et al. 1991), soil (AOAC 1984; Czuczwa and Alford-Stevens 1989; EPA 1986b; Lopez-Avila et al. 1989a, 1990b; Noegrohati and Hammers 1992; Schuphan et al. 1990), food (AOAC 1984; Bernal et al. 1992; Liao et al. 1991; Long et al. 1991a, 1991b; Muino et al. 1991; Noegrohati and Hammers 1992; Schmidt and Hesselberg 1992; Tonogai et al. 1989; Venant et al. 1989), milk (DiMuccio et al. 1988; Kapoor et al. 1981), tobacco (Waliszewski and Szymczynski 1986), and wood preserving fluid (Butte and Walker 1992). These methods are sensitive enough to measure background levels in environmental media. The precision, accuracy, reliability, and specificity of these methods are sufficiently documented. Research investigating the relationship between levels measured in air, water, soil, and food and observed health effects could increase our confidence in existing methods and/or indicate where improvements are needed.

6.3.2 Ongoing Studies

New methodology for improving multiple pesticide analyses of short-life residues in processed foods is being developed at the University of Tennessee, in Knoxville (L. Melton, investigator).

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding α-, β-, γ-, and δ-HCH in air, water, and other media are summarized in Table 7-1. Unless otherwise specified, the regulations in the table refer to HCH in general (all isomers).

EPA (IRIS 1998) assigned γ-HCH an oral reference dose (RfD) of 3.00×10^{-4} mg/kg/day with an uncertainty factor of 1,000 based on liver and kidney toxicity in rats (Zoecon Corporation 1983).

EPA (IRIS 1998) has assigned the following weight-of-evidence classifications: α-HCH is assigned a classification of B2 (probable human carcinogen); β-HCH is assigned a classification of C (possible human carcinogen); γ-HCH is among those substances being evaluated by the EPA for evidence of human carcinogenicity; and δ-HCH is assigned a classification of D (not classifiable as to human carcinogenicity).

EPA estimates that concentrations of α-HCH in water of 0.6, 0.06, and 0.006 µg/L are associated in humans with excess lifetime cancer risks of 10^{-4}, 10^{-5}, and 10^{-6}, respectively, and that concentrations of β-HCH in water of 2, 0.2, and 0.02, µg/L are associated in humans with excess lifetime cancer risks of 10^{-4}, 10^{-5}, and 10^{-6}, respectively (IRIS 1998).

γ-HCH is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Right-to-Know Act of 1986" (EPA 1991h, 1988f).

Tolerances are established for γ-HCH in or on raw agricultural commodities as follows: 7 ppm in or on the fat of meat from cattle, goats, horses, and sheep; 4 ppm in or on the fat of meat from hogs; 3 ppm in or on cucumbers, lettuce, melons, pumpkin, squash, summer squash, and tomatoes; and 1 ppm in or on apples and apricots (EPA 1974a, 1974b).

The use of γ-HCH has been restricted by EPA since 1977 and is to be applied only by a certified applicator (EPA 1985b).

TABLE 7-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane

Agency	Description	Information	References
INTERNATIONAL			
FAO/WHO	ADI 0.0–0.1 mg/kg	WHO 1976; FAO/ body weight	WHO 1978
	Allowable tolerances (γ-HCH)		WHO 1976
	Potatoes	0.05 mg/kg	
	Lettuce	2.0 mg/kg	
IARC	Carcinogenic classification	Group 2B[a]	IARC 1987
WHO	Guidelines for drinking water	0.003 mg/L	WHO 1984
NATIONAL			
Regulations:			
a. Air: OSHA	PEL TWA (skin designation)(γ-HCH)	0.5 mg/m^3	OSHA 1998 (29 CFR 1910.1000); OSHA 1989b
	Meets criteria for OSHA medical records rule (α-HCH, γ-HCH)	Yes	OSHA 1987 (29 CFR 1910.20); OSHA 1988
b. Water: EPA ODW	Regulated under the SDWA of 1986; drinking water quality standard (γ-HCH)	4 µg/L	FSTRAC 1990
EPA OWRS	General pretreatment regulations for existing and new sources of pollution	Yes	EPA 1988b (40 CFR 403, Appendix B); EPA 1988c
c. Food: FDA	Permissible levels in bottled water	0.004 mg/L	FDA 1989a (21 CFR 103.35); FDA 1982b
EPA	Tolerance for residues (γ-HCH):		EPA 1998 (40 CFR 180.133)
	in or on the fat of meat from cattle, goats, horses,and sheep	7 mg/kg	
	in or on the fat of meat from hogs	4 mg/kg	
	in or on cucumbers, lettuce, melons, mushrooms, pumpkin, squash, summer squash, and tomatoes	3 mg/kg	
	in or on apples, apricots, asparagus, avocados, broccoli, brussel sprouts, cabbage, cauliflower, celery, cherries, collards, eggplants, grapes, gauvas, kale, kohlrabi, mangoes, mustard greens, nectarines, okra, onions (dry bulb only), peaches, pears, peppers, pineapples, plums (fresh prunes), quinces, spinach, strawberries, and Swiss chard	1 mg/kg	
	in or on pecans	0.01 mg/kg	
d. Other: DOT	Hazardous Material Transportation Act: γ-HCH is designated as a hazardous materials which is subject to requirements for packaging, shipping and transporting.	Yes	DOT 1989a (49 CFR 172.101, Appendix A); DOT 1989b

TABLE 7-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane (*continued*)

Agency	Description	Information	References
NATIONAL (Cont.)			
EPA OERR	Reportable quantity (γ-HCH)	1 pound	EPA 1996a (40 CFR 302.4); EPA 1998
	Extremely hazardous substances Threshold Planning Quantity (γ-HCH)	1,000/10,000 pounds	EPA 1996b (40 CFR 355, Appendix A); EPA 1998
EPA OSW	Designated as a hazardous substance (γ-HCH)	Yes	EPA 1996c (40 CFR 302.4); EPA 1998
	Designated as a hazardous pollutant under section 311(b)(2)(A) of the Federal Water Pollution Control Act (γ-HCH)	Yes	EPA 1996d (40 CFR 116.4); EPA 1998
	Designated as a toxic pollutant under Section 307(a)(1) of the Federal Water Pollution Act (γ-HCH)	Yes	EPA 1996e (40 CFR 401.15); EPA 1979b
	Groundwater monitoring requirement (γ-HCH)/Maximum concentration	Yes/0.004 mg/L	EPA 1987e (40 CFR 264.94); EPA 1987f
	Listing as a hazardous waste; discarded commercial chemical products, manufacturing chemical intermediates, or off-specification commercial chemical products (γ-HCH)	No	EPA 1996f (40 CFR 261.33); EPA 1998
	Listing as a hazardous constituent (γ-HCH)	Yes	EPA 1998(40 CFR 261, Appendix VIII); EPA 1998
	Maximum concentration of contaminants for the toxicity characteristic (γ-HCH)	0.4 mg/L	EPA 1998(40 CFR 261.24); EPA 1990d
EPA OTS	Toxic release reporting; Community Right-to-Know (γ-HCH)	Yes	EPA 1998 (40 CFR 372)
Guidelines:			
a. Air:			
ACGIH	TLV TWA (skin designation) (γ-HCH)	0.5 mg/m^3	ACGIH 1998
NIOSH	REL TWA (skin designation) (γ-HCH)	0.5 mg/m^3	NIOSH 1998
b. Water:			
EPA ODW	MCL in drinking water (γ-HCH)	0.0002 mg/L	EPA 1996
	MCLG in drinking water (γ-HCH)	0.0002 mg/L	
	Health advisories (γ-HCH)		
	1-day	1.0 mg/L	
	10-day	1.0 mg/L	
	Longer term (child)	0.03 mg/L	
	Longer term (adult)	0.1 mg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane (*continued*)

Agency	Description	Information	References
NATIONAL (Cont.)			
	Lifetime	0.2×10^{-4} mg/L	
	RfD	3.0×10^{-4} mg/L	
	DWEL	0.01 mg/L	
EPA OWRS	Ambient water quality criteria for protection of human health:		EPA 1996j (40 CFR 130)
	Ingesting water and organisms		
	α-HCH	3.9×10^{-3} µg/L	
	β-HCH	1.4×10^{-2} µg/L	
	γ-HCH	1.9×10^{-2} µg/L	
	Ingesting of organisms only		
	α-HCH	1.3×10^{-2} µg/L	
	β-HCH	4.6×10^{-2} µg/L	
	γ-HCH	6.3×10^{-2} µg/L	
	Ambient water quality criteria for protection of aquatic life:		
	freshwater (γ-HCH)		
	acute	2.0 µg/L	
	chronic	8.0×10^{-2} µg/L	
	saltwater (γ-HCH)		
	acute	1.6×10^{-1} µg/L	
NAS	SNARL	(γ-HCH)	NAS 1982
	7 day	0.5 mg/L	
	24 hours	3.5 mg/L	
c. Other EPA			IRIS 1998
	α-HCH		
	Carcinogenic classification	Group B2[b]	
	Unit risk (air)	1.8×10^{-3} $(\mu g/m^3)^{-1}$	
	Unit risk (water)	1.8×10^{-4} $(\mu g/L)^{-1}$	
	β-HCH		
	Carcinogenic classification	Group C[c]	
	Unit risk (air)	5.3×10^{-4} $(\mu g/m^3)^{-1}$	
	Unit risk (water)	5.3×10^{-5} $(\mu g/L)^{-1}$	
	δ-HCH		
	Carcinogenic classification	Group D[d]	
	γ-HCH		
	RfD (oral)	3.00×10^{-4} (mg/kg/day)$^{-1}$	
	Carcinogenic classification	Under review	
	Technical-HCH		
	Carcinogenic classification	B2[b]	
	Unit risk (air)	5.1×10^{-4} $(\mu g/m^3)^{-1}$	
	Unit risk (water)	5.1×10^{-5} $(\mu g/L)^{-1}$	
NTP	α-HCH, β-HCH, γ-HCH, technical grade	Reasonably anticipated to be carcinogens	NTP 1991

TABLE 7-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane (*continued*)

Agency	Description	Information	References
STATE			
Regulations and Guidelines:			
a. Air:			
	Acceptable ambient air concentrations		NATICH 1996
	α-HCH		
Arizona	(1 hour)	1.10 μg/m^3	
Arizona	(24 hours)	3.00x10^{-1} μg/m3	
Arizona	(Annual)	8.10x10^{-4} μg/m^3	
Florida-Tampa	(8 hours)	5.00x10^{-3} mg/m^3	
Florida-Fort Lauderdale	(8 hours)	5.00x10^{-3} mg/m^3	
Florida-Pinellas	(Annual)	5.60x10^{-4} μg/m^3	
New York	(Annual)	1.67 μg/m^3	
Pennsylvania-Philadelphia	(Annual)	1.20 μg/m^3	
	β-HCH		
Arizona	(1 hour)	1.10 μg/m^3	
Arizona	(24 hours)	3.00x10^{-1} μg/m^3	
Arizona	(Annual)	8.10x10^{-4} μg/m^3	
Florida-Pinellas	(Annual)	1.90x10^{-3} μg/m^3	
	γ-HCH		
Arizona	(1 hour)	1.10 μg/m^3	
Arizona	(24 hours)	3.00x10^{-1} μg/m^3	
Arizona	(Annual)	8.10x10^{-4} μg/m^3	
Connecticut	(8 hours)	5.00 μg/m^3	
Florida-Tampa	(8 hours)	5.00x10^{-3} mg/m^3	
Florida-Fort Lauderdale	(8 hours)	5.00x10^{-3}mg/m^3	
Florida-Pinellas	(8 hours)	5.00 μg/m^3	
Florida-Pinellas	(24 hours)	1.20 μg/m^3	
Kansas	(Annual)	3.33x10^{-3} μg/m^3	
Massachusetts	(24 hours)	1.40x10^{-1} μg/m^3	
Massachusetts	(Annual)	3.00x10^{-3} μg/m^3	
Nevada	(8 hours)	1.20x10^{-2} mg/m^3	
North Dakota	(8 hours)	5.00x10^{-3} mg/m^3	
New York	(Annual)	1.67 μg/m^3	
Oklahoma	(24 hours)	5.00 μg/m^3	
Pennsylvania-Philadelphia	(Annual)	1.20 μg/m^3	
South Carolina	(24 hours)	5.00 μg/m^3	
Texas	(30 minutes)	5.00 μg/m^3	
Texas	(Annual)	5.00x10^{-1} μg/m^3	
Virginia	(24 hour)	8.30 μg/m^3	
Washington-Southwest	(24-hour)	1.60 μg/m^3	
	technical-HCH		
Arizona	(1 hour)	1.10 μg/m^3	
Arizona	(24 hours)	3.00x10^{-1} μg/m^3	
Arizona	(Annual)	8.10x10^{-4} μg/m^3	
Kentucky	Significant emission levels of toxic air pollutants	1.276x10^{-4} pounds per hour	NREPC 1986 (401 KAR 63.022)

TABLE 7-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane (*continued*)

Agency	Description	Information	References
STATE (Cont.)			
Wisconsin	Hazardous air contaminant without acceptable ambient concentrations; lowest achievable emission rate	25 pounds/year[2]	WAC 1988
b. Water:			
	Drinking water quality criteria	0.0002 mg/L	
Alabama			AL DEM 1998
Colorado			CO DHWQD 1998
Connecticut			CT DEP 1998
Delaware			DE NREC 1998
Florida			FL DEP 1998
Georgia			GA DNR 1998
Idaho			ID DHW 1998
Illinois			IL EPA 1998
Indiana			IN OWM 1998
Iowa			IA DNR 1998
Kansas			KS DHE 1998
Kentucky			KY EPD 1998
Maine			ME DEP 1998
Maryland			MD DNR 1998
Massachusetts			MA DEP 1998
Michigan			MI DNR 1998
Minnesota			MN PCA 1998
Missouri			MO DNR 1998
Montana			MT DHES 1998
Nebraska			NE DEQ 1998
New Hampshire			NH DES 1998
New Mexico			NM ED 1998
Oklahoma			OK WRB 1998
Oregon			OR DEQ 1998
Rhode Island			RI DEM 1998
South Carolina			SC DHEC 1998
South Dakota			SD DENR 1998
Texas			TX NR 1998
Washington			WA DE 1998
West Virginia			WV DEP 1998
Wyoming			WY DEQ 1998
New York		0.004 mg/L	NY DEC 1998
North Dakota			ND DH 1998
	Surface water quality standards; aquatic life habitat		
Delaware	Acute	2.0 µg/L	DE NREC 1998
Delaware	Chronic	0.08 µg/L	
Hawaii	Acute	2.0 µg/L	HI CWB 1998
Hawaii	Chronic	0.08 µg/L	
Kentucky	Acute	2.0 µg/L	KY EPD 1998
Kentucky	Chronic	0.08 µg/L	
Louisiana	Acute	2.00 µg/L	LA DEQ 1998
Louisiana	Chronic	0.08 µg/L	
Maryland	Acute	2.0 µg/L	MD DNR 1998

TABLE 7-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane (*continued*)

Agency	Description	Information	References
STATE (Cont.)			
Maryland	Chronic	0.08 µg/L	
Nevada		0.002 mg/L	NV DCNR 1998
New Jersey	Acute	2.0 µg/L	NJ DEP 1998
	Chronic	0.08 µg/L	
North Carolina		0.01 µg/L	NC DEHNR 1998
South Dakota	Acute	2.0 µg/L	SD DENR 1998
South Dakota	Chronic	0.08 µg/L	
Vermont	Acute	2.0 µg/L	VT ANR 1998
Vermont	Chronic	0.08 µg/L	
Wisconsin	Human threshold criteria		WDNR 1987
	α-HCH		
	Public water supply:		
	Warm water sport fish communities	0.07 µg/L	
	Cold water communities	0.033 µg/L	
	Great Lakes communities	0.034 µg/L	
	Non-water supply:		
	Warm water sport fish communities	0.15 µg/L	
	Cold water communities	0.045 µg/L	
	Warm water forage and limited forage fish communities and limited aquatic life	26 µg/L	
	β-HCH		
	Public water supply:		
	Warm water sport fish communities	0.12 µg/L	
	Cold water communities	0.059 µg/L	
	Great Lakes communities	0.06 µg/L	
	Non-water supply:		
	Warm water sport fish communities	0.027 µg/L	
	Cold water communities	0.079 µg/L	
	Warm water forage and limited forage fish communities and limited aquatic life	46 µg/L	
	γ-HCH		
	Public water supply:		
	Warm water sport fish communities	0.14 µg/L	
	Cold water communities	0.067 µg/L	
	Great Lakes communities	0.068 µg/L	
	Non-water supply:		
	Warm water sport fish communities	0.03 µg/L	
	Cold water communities	0.09 µg/L	
	Warm water forage and limited forage fish communities and limited aquatic life	53 µg/L	
	HCH-technical grade		
	Public water supply:		
	Warm water sport fish communities	0.094 µg/L	
	Cold water communities	0.044 µg/L	
	Great Lakes communities	0.045 µg/L	
	Non-water supply:		
	Warm water sport fish communities	0.02 µg/L	
	Cold water communities	0.06 µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane (*continued*)

Agency	Description	Information	References
STATE (Cont.)			
Wisconsin	Warm water forage and limited forage fish communities and limited aquatic life	35 µg/L	
c. Other	Restricted use of pesticide. Special requirements on registration, permits, labeling, application, storage, disposal record keeping and/or reporting.		CELDS 1993
Alabama Arkansas Arizona California Colorado Connecticut Delaware Florida Georgia Hawaii Kansas Kentucky Illinois Iowa Maine Maryland Massachusetts Michigan Minnesota Missouri Montana Nevada New Hampshire New Jersey New Mexico New York North Carolina North Dakota Ohio Oklahoma Oregon Pennsylvania South Carolina South Dakota Utah Vermont Virginia Washington Wisconsin Wyoming			
Alabama	Groundwater protection; hazardous waste discharge	0.004 µg/L	CELDS 1993

TABLE 7-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane (*continued*)

Agency	Description	Information	References
STATE (Cont.)			
California		0.004 µg/L	CELDS 1993
Colorado		Not specified	
Delaware		Not specified	
Kentucky		0.004 µg/L	
Louisiana		Not specified	
Massachusetts		0.004 µg/L	
Minnesota		Not specified	
Nebraska		0.004 µg/L	
New Jersey		0.004 µg/L	
New York		Not detectable	
North Carolina		0.004 µg/L	
North Dakota		Not specified	
Oregon		0.004 µg/L	
South Carolina		0.004 µg/L	
Tennessee		0.004 µg/L	
Texas		0.004 µg/L	
Utah		0.004 µg/L	
Wisconsin		0.001 mg/L	
Alabama Nebraska North Carolina Tennessee Vermont Virginia	Groundwater protection; EP toxicity	0.4 mg/L	CELDS 1993
Arizona Florida Missouri Nebraska Nevada Ohio Utah	Water quality criteria for agricultural use, recreation, wildlife and/or fish		CELDS 1993
Colorado Illinois Louisiana Massachusetts Minnesota North Dakota Vermont West Virginia	Hazardous waste criteria for lindane		CELDS 1993

TABLE 7-1. Regulations and Guidelines Applicable to Hexachlorocyclohexane (*continued*)

Agency	Description	Information	References
STATE (Cont.)			
Wisconsin			

[a]Group 2B: Possible human carcinogen
[b]Group B2: Probable human carcinogen
[c]Group C: Possible human carcinogen
[d]Group D: Not classifiable as to human carcinogenicity

ACGIH = American Conference of Governmental Industrial Hygienists; ADI = Acceptable Daily Intake; DOT = Department of Transportation; EPA = Environmental Protection Agency; FAO = Food and Agriculture Organization; FDA = Food and Drug Administration; HCH = Hexachlorocyclohexane; IARC = International Agency for Research on Cancer; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NAS = National Academy of Science; ND = Not Determined; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; RfD = Reference dose; SDWA = Safe Drinking Water Act; SNARL = Suggested No Adverse Response Effect Level; TLV = Threshold Limit Value; TWA = Time Weighted Average; WHO = World Health Organization

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9. GLOSSARY

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level—An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen—A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL)—An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL)—The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50})—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF)—A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

9. GLOSSARY

APPENDIX A

ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: γ-HCH
CAS Number: 58-89-9
Date: January 15, 1999
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 9
Species: Rat

Minimal Risk Level: 0.01 [X] mg/kg/day [ ] ppm

Reference: Joy et al. 1982

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Groups of 7-14 male Sprague-Dawley rats were exposed by gavage to 0, 1, 3, or 10 mg/kg/day lindane in corn oil for up to 23 days. Kindling (development of seizures with repeated application of initially subthreshold electrical stimuli) was performed.

Effects noted in study and corresponding doses: Electronic amygdaloid stimulation to induce epileptic-like seizures had a significant effect on number of rats with electrical after discharges exhibiting behavioral responses given the 3 mg/kg/day dose for 4 days. Significant changes in most indices (number of stimulations required to give a behavioral response, number of stimulations evoking an afterdischarge until subjects showed first generalized epileptic response) were seen at 3 mg/kg/day after 23 days.
Calculations: 1 mg/kg/day X 1/100UF = 0.01 mg/kg/day.

Dose and endpoint used for MRL derivation:

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
If so, explain: No

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Other additional studies or pertinent information which lend support to this MRL:
Rats exposed by gavage to 2.97 mg/kg/day lindane for 6 days exhibited increased pineal N-acetyl-transferase and decreased serotonin levels (Attia et al. 1991). Serrano et al. (1990a) exposed rats to 5 mg/kg/day γ-HCH by oil gavage for 3 days, resulting in decreased myelin and 2',3'-cyclic nucleotide 43'-phosphodiesterase activity in the brain. Seizures and convulsions have been reported in humans following ingestion of γ-HCH

(Davies et al. 1983; Harris et al. 1969; Munk and Nantel 1977; Powell 1980; Starr and Clifford 1972; Storen 1955).

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: β-HCH
CAS Number: 319-85-7
Date: January 15, 1999
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 9
Species: Mouse

Minimal Risk Level: 0.2 [X] mg/kg/day [ ] ppm

Reference: Cornacoff et al. 1988

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Groups of 6 female B6C3F1 mice were treated with 0, 100, 300, or 1000 ppm beta-HCH in the diet for 30 days (0, 19, 57, or 190 mg/kg/day).

Effects noted in study and corresponding doses: Mice receiving 57 or 190 mg/kg/day exhibited ataxia within 1 week. The signs were resolved in a few days in the 57 mg/kg/day group, but 80% of mice in the 190 mg/kg/day group became laterally recumbant and were euthanized. No ataxia was seen at 19 mg/kg/day.

Dose and endpoint used for MRL derivation: 19 mg/kg/day (100 ppm); ataxia.
Calculations: 19 mg/kg/day X 1/100UF = 0.19 mg/kg/day.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
If so, explain: Yes. A food factor of 0.19 kg feed/kg body weight/day for female $B6C3F_1$ mice was used to convert dose from mg/kg (ppm) food to mg/kg body weight as follows: 100 ppm X 0.19 (mouse food factor) = 19 mg/kg/d; 300 ppm = 57 mg/kg/d; 1000 ppm = 190 mg/kg/day.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Other additional studies or pertinent information which lend support to this MRL:
A study by Hulth et al. (1978) in which female NMRI mice were exposed once orally to alpha-HCH also found neurological effects in the form of increased convulsive threshold and increased brain GABA levels at 150 mg/kg/day. A significant reduction in motor conduction velocity in tail nerve was seen in Wistar rats exposed orally to 66 mg/kg/day beta-HCH for 30 days (Muller et al. 1981). Rats treated with 12.5 mg/kg/day beta-HCH in food for 13 weeks underwent early autopsy due to progressive clinical signs (e.g., ataxia followed by coma) (Van Velsen et al. 1986).

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: α-HCH
CAS Number: 319-84-6
Date: January 15, 1999
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 61
Species: Rat

Minimal Risk Level: 0.008 [X] mg/kg/day [ ] ppm

Reference: Fitzhugh et al. 1950 (Table 2 of the article).

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Groups of 10 male and 10 female Wistar rats were treated with 0, 10, 50, 100, or 800 ppm alpha-HCH in food (0.8, 4, 8, or 64 mg/kg/day) for the lifespan. The mean age at death of the 10 ppm group (NOAEL) was 54.6 weeks and of the control group was 58.3 weeks. The lifetime of the animals sacrificed at the end of the experiment was taken as 107 weeks. Body weight, organ weight, and histopathological changes were monitored.

Effects noted in study and corresponding doses: Body weight decreased significantly compared to controls in males (18%) and females (13%) at 800 ppm (64 mg/kg/day). A significant decrease (38%) in age at death was seen at 80 mg/kg/day. A significant increase in relative liver weight (36%) was seen at 50 ppm (4 mg/kg/day). Slight microscopic liver damage (diffuse cell enlargement, focal necrosis, fatty degeneration) was seen at 50 ppm (4 mg/kg/day), and slight kidney damage (focal nephritis) was seen at 800 ppm (64 mg/kg/day).

Dose and endpoint used for MRL derivation: 0.8 mg/kg/day (10 ppm); no hepatic effects.
Calculations: 0.8 mg/kg/day × 1/100UF = 0.008 mg/kg/day.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
If so, explain: Yes. A food factor of 0.08 kg feed/kg body weight/day for female Wistar rats was used to convert dose from ppm food to mg/kg body weight as follows: 10 ppm × 0.08 (rat food factor) = 0.8 mg/kg/day; 50 ppm = 4 mg/kg/day; 100 ppm = 8 mg/kg/day; 800 ppm = 64 mg/kg/day.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Other additional studies or pertinent information which lend support to this MRL:Other studies have observed various hepatic effects after chronic-duration oral exposure to alpha and other HCH isomers (Amyes et al. 1990; NCI 1977; Wolff et al. 1987; Ito et al. 1975; Thorpe and Walker 1973; Munir et al. 1983; Kashyap et al. 1979). Amyes et al. observed periacinar hypertrophy in male and female Wistar rats treated with 8 mg/kg/day γ-HCH in their diet for up to 52 weeks. The NOAEL was determined to be 0.8 mg/kg/day. Hepatocellular carcinoma was observed in rats fed 50 mg/kg/day α-HCH in their diet for 72 week (Ito et al. 1975). Hepatocellular carcinoma was also reported in mice treated with 34 mg/kg/day β-HCH in their diet for 104 weeks (Thorpe and Walker 1973).

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: β-HCH
CAS Number: 319-85-7
Date: January 15, 1999
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 22
Species: Rat

Minimal Risk Level: 0.0006 [X] mg/kg/day [ ] ppm

Reference: Van Velsen et al. 1986

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Groups of 10 male and 10 female Wistar rats were treated with 0, 2, 10, 50. or 250 ppm beta-HCH in food for 13 weeks (0, 0.18, 0.9, 4.5, or 22.5 mg/kg/day), then sacrificed.

Effects noted in study and corresponding doses: Hyalinization of centrilobular cells, indicating the initiation of hepatic effects, was observed at the low dose (2 ppm or 0.18 mg/kg/day). An increase in cellular hypertrophy and number of eosinophils was seen at 2 ppm (0.18 mg/kg/day). Centrilobular hepatocytic hypertrophy and proliferation of smooth endoplasmic reticulum were seen at the high dose in 8/9 animals. A dose-dependent increase in liver weight was seen at 10 ppm (0.9 mg/kg/day) and above.

Dose and endpoint used for MRL derivation: 0.18 mg/kg/day; hyalinization of centrilobular cells.
Calculations: 0.18 mg/kg/day X 1/300UF = 0.0006 mg/kg/day.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
If so, explain: Yes. A food factor of 0.09 kg feed/kg body weight/day for male Wistar rats was used to convert from ppm in food to mg/kg as follows: 2 ppm X 0.09 (rat food factor) = 0.18 mg/kg/day; 10 ppm = 0.9 mg/kg/day; 50 ppm = 4.5 mg/kg/day; 250 ppm = 22.5 mg/kg/day.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Other additional studies or pertinent information which lend support to this MRL: Significant increases in liver weight and the levels of hepatic cytochrome P-450, triglycerides, phospholipids, and cholesterol were seen in rats fed 50 mg/kg/day β-HCH for 2 weeks (Ikegami et al. 1991a, 1991b). Liver hypertrophy was seen in rats fed 25 mg/kg/day for 24 weeks (Ito et al. 1975), and in mice fed 32.5 mg/kg/day for 24 weeks (Ito et al. 1973). Fatty degeneration and necrosis were seen in liver of mice fed 0.5-40 mg/kg/day for up to

53 weeks (Fitzhugh et al. 1950). Schöter et al. (1987) also observed an increase in hepatic foci in rats exposed to 3 mg/kg/day in the diet for 20 weeks.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: γ-HCH
CAS Number: 58-89-9
Date: January 15, 1999
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 29
Species: Mouse

Minimal Risk Level: 0.00001 [X] mg/kg/day [ ] ppm

Reference: Meera et al. 1992

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Groups of 6 female Swiss mice were exposed in the diet to 0, 0.012, 0.12, or 1.2 mg/kg/day γ-HCH for up to 24 weeks.

Effects noted in study and corresponding doses: A dose-dependent biphasic response (stimulation followed by suppression) in cell-mediated and humoral components of the immunological profile was seen. *In vitro* splenic lymphocyte transformation in response to the mitogen Con A showed a faster onset of proliferative response (4 weeks) at doses 0.12 and 1.2 mg/kg, with an onset of 8 weeks at 0.12 mg/kg. Dose-dependent increase in size of thymus medulla, and decrease in cellular population of cortex was also seen.

Dose and endpoint used for MRL derivation: 0.012 mg/kg/day; reduced activity of lymphoid follicles with prominent megakaryocytes and delayed hypersensitivity to immune challenge.
Calculations: 0.012 mg/kg/day X 1/1000UF = 0.00001 mg/kg/day.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
If so, explain: Yes. Conversions performed by authors of the study—details not provided.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Other additional studies or pertinent information which lend support to this MRL: Immunosuppression in the form of reduced antibody response to *Salmonella* challenge was seen in rats exposed to 6.25 mg/kg/day gamma-HCH for up to 5 weeks (Dewan et al. 1980). Acute oral exposures of mice to 10 mg/kg/day gamma-HCH for 10 days resulted in residual bone marrow damage and suppressed granulocyte-macrophage progenitor cells, while at 3-day exposures to 40 mg/kg/day, thymus cortex atrophy was also seen (Hong and Boorman 1993).

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an

inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-1).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects.

The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

SAMPLE

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
INTERMEDIATE EXPOSURE							
5	6	7	8	9			10
Systemic							
18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
38	Rat	18 mo 5d/wk 7hr/d			9 20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

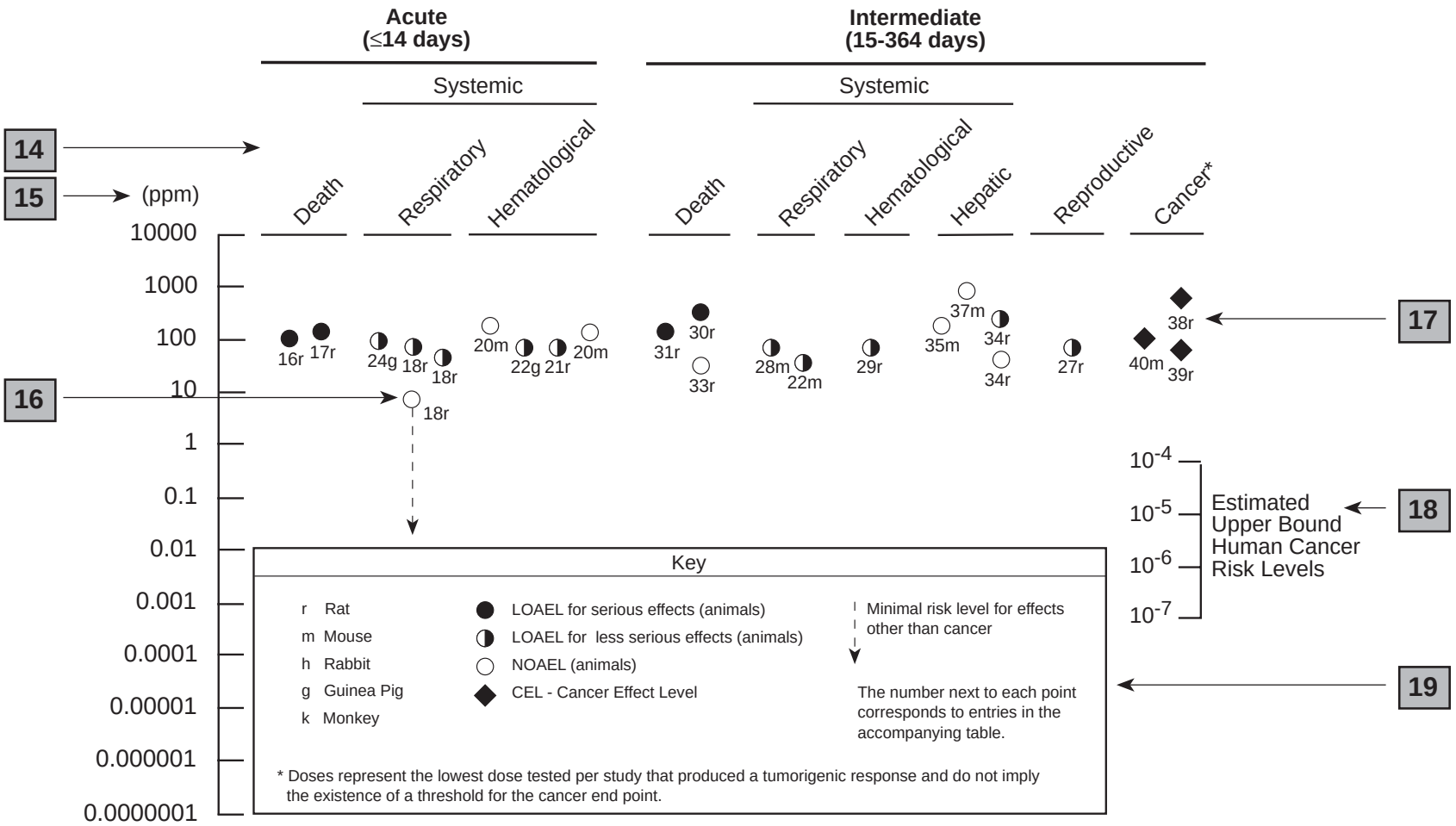
[a] The number corresponds to entries in Figure 2-1.

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

Relevance to Public Health

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient

L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio

STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
µm	micrometer
µg	microgram